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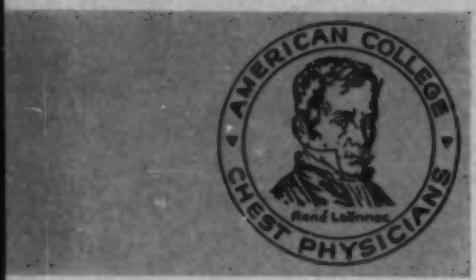
DISEASES of the CHEST



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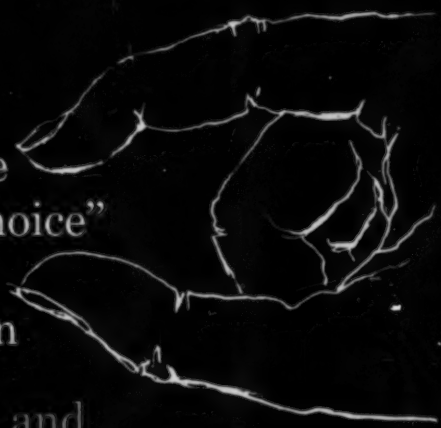

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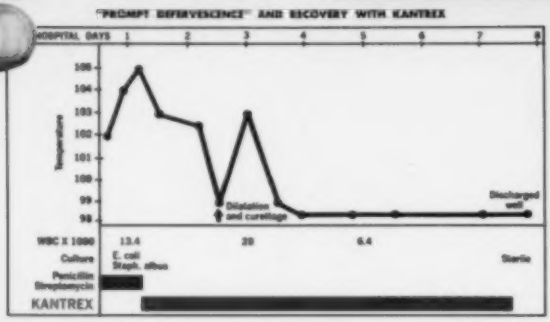


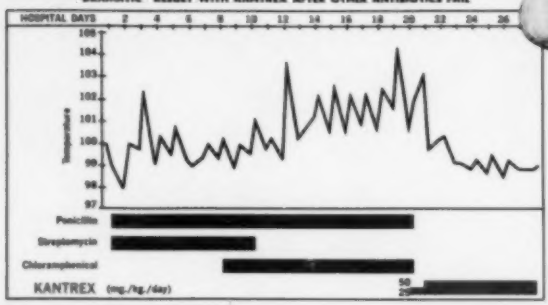
. . . in genito-urinary infections *(due to staph or "gram-negatives")*

N. A., a 27-year-old female with postabortal sepsis due to *E. coli* and *Staph. albus* had "prompt defervescence" and recovery with KANTREX after 2 other antibiotics had proved ineffective. No toxic effects were observed.

—Rosenburg, A. M., Kosta, G. M., and Schweinburg, F. B.: Annals N.Y. Acad. Sci. 76:348, 1958

APPENDICEAL ABSCESS

"DRAMATIC" RESULT WITH KANTREX AFTER OTHER ANTIBIOTICS FAIL



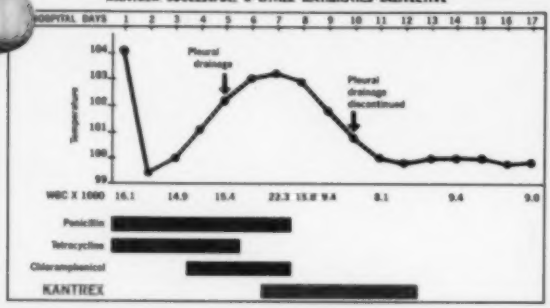
. . . in skin, soft tissue and post-surgical infections *(due to staph or "gram-negatives")*

J. H. W., 12-year-old boy with appendiceal abscess due to *Staph. aureus*, showed a "clear-cut" and "dramatic" response to KANTREX after 3 other antibiotics had failed. No toxic reactions were noted.

—Yow, E. M., and Hinman, O. T.: Annals N.Y. Acad. Sci. 76:472, 1958

STAPH PNEUMONIA

KANTREX SUCCESSFUL; 3 OTHER ANTIBIOTICS INEFFECTIVE



. . . in respiratory tract infections *(due to staph or "gram-negatives")*

T. A., a 4-week-old female infant with pneumonia, pyoderma and septicemia due to *Staph. aureus* showed a prompt beneficial effect and uneventful recovery with KANTREX after 3 other antibiotics had proved unsuccessful. "No serious untoward reactions were observed."

—Riley, H. D. Jr.: Antibiotics Annual 1958-1959, p. 623.

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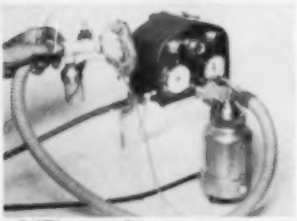

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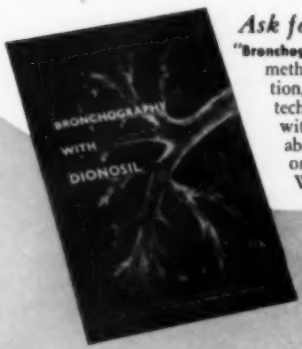

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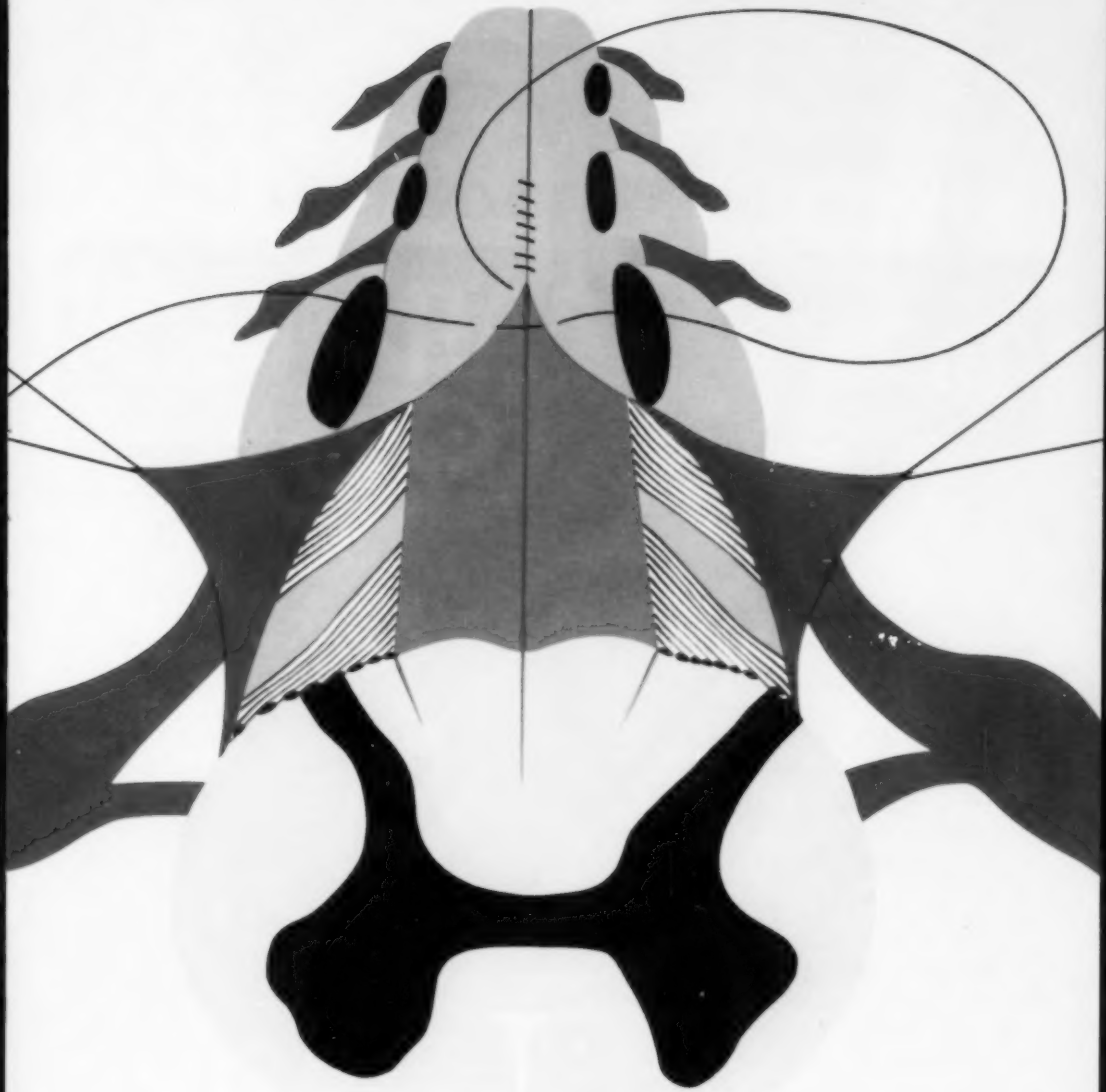

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28	20,000	33,000
29	20,000	30,000
30	20,000	27,000
31	20,000	24,000
32	20,000	22,000
33	20,000	
34	19,064	
35	18,068	
36	17,042	
37	16,096	
38	15,174	
39	14,260	
40	13,410	
41	12,586	
42	11,794	
43	11,040	
44	10,320	
45	9,634	
46	8,990	
47	8,372	
48	7,798	
49	7,246	
50	6,736	
51	6,254	
52	5,802	
53	5,378	
54	4,982	
55	4,614	
56	4,272	
57	3,952	
58	3,656	
59	3,378	
60	3,122	
61	2,844	
62	2,662	
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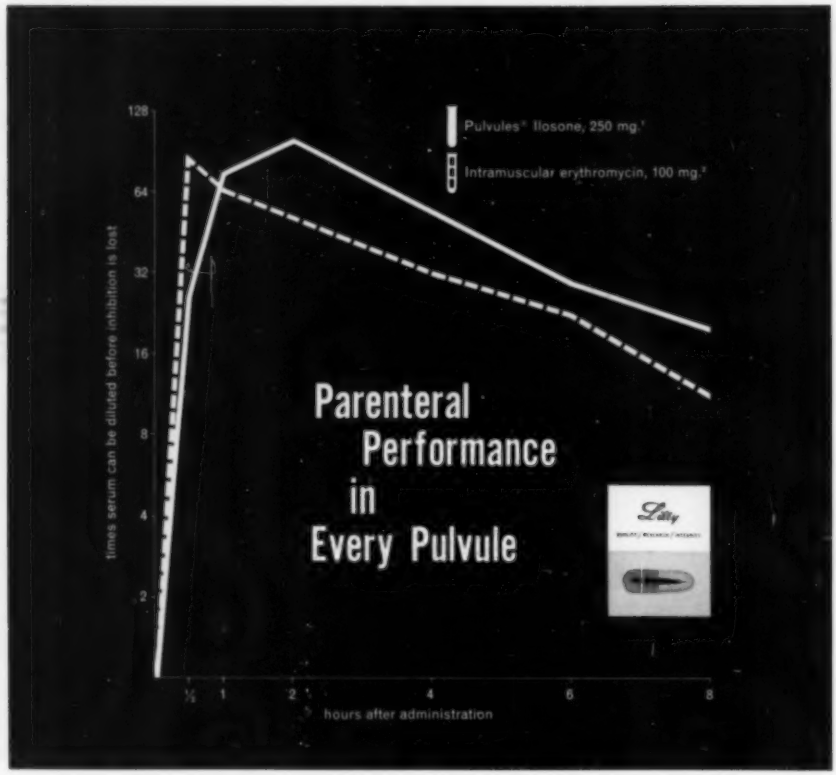

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1. Antibiotic Med. & Clin. Therapy, *5*:609, 1958.
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DISEASES of the CHEST

VOLUME XXXVI JULY, 1959 NUMBER 1

Clinic Experience with a Urine PAS Test

ERNEST RICHARD PITMAN, M.D., F.C.C.P.,
E. EDWARD BENZIER, M.D., F.C.C.P., and MELVIN KATZ, M.D.
New York, New York

Para-aminosalicylic acid is frequently used in conjunction with other antituberculous agents in the combined therapy of tuberculosis. Many patients do not tolerate PAS in adequate doses because of side effects or the inconvenience of ingesting many tablets of relatively large size throughout the day. Furthermore, it is the general experience among physicians working with tuberculous patients that many who do not take the drug do not inform their physicians of this fact or vigorously deny their lack of adherence to a prescribed program. Recently we noted in the literature[1] a test suitable for the detection of PAS or its decomposition products in the urine for patients on an outpatient basis. The results of this test are the basis of the following report.

The patients investigated were those taking PAS as part of the drug therapy regimen outlined by the New York City Health Department, Bureau of Tuberculosis for use in its chest clinics.[2] In the Kips Bay Chest Clinic there were 61 such patients who were taking PAS as part of their drug therapy and who were found suitable for study. They ranged in age from 22 to 66. There were 44 men and 17 women. Of the patients 52 were white, two were Negro, three were Puerto Rican and four were Chinese. The men were predominately over age 45. In the women the 20-35 age group were predominant.

Methods

The test used is as follows: 0.5 ml. of standard Erlich's reagent (0.7 gm. of p-dimethylamino-benzaldehyde in a mixture of 150 ml. of conc. HCL and 100 ml. of H_2O) is added drop by drop to 5 ml. of urine. PAS can be detected by the immediate development of a lemon-yellow color, with an orange or yellow precipitate if there is much PAS (i.e., about 1%). In practice it has been found that if the patient has taken his PAS in the dosage range prescribed (4 grams T.I.D.) the previous night, the test was sensitive to detect PAS in the first morning specimen. However, the second specimen might be negative unless the morning dose of PAS had been taken.

Using this test, the study was conducted in the following manner. The patients, as is the usual custom, were asked by the nurse if they had been taking their medication since their last visit to the clinic. (Patients are usually seen every two months while on drug therapy.)

Department of Health, Bureau of Tuberculosis, Kips Bay Chest Clinic.

Results

Of the 61 cases studied by the urine test, 36 gave a positive reaction; as shown by the development of an orange or yellow precipitate in the urine Twenty-five gave a negative test. All who were negative reactors admitted upon questioning that they were taking PAS intermittently, irregularly, or not at all. In the positive urine test group, all were recalled for questioning. The physician used the same vigorous technique as was used on the negative group. Four of the 36 upon questioning admitted not taking their PAS regularly.

DISCUSSION

A positive urine test for PAS only indicates that the patient took his medication the night before, or the morning of his clinic visit. Thus, it is important to repeat the test at different times in order to detect the patient who does not take his PAS as ordered.

Our experience would suggest that Standard Erlichs Reagent added to the urine of the patient on PAS therapy can be used as a screening test to determine whether the patient is taking his medication. Only the sulfonamide group will interfere with this test. The test is simple, inexpensive and can be done by a clinical aide with a minimum of training.

In any study of drug therapy using PAS, it is important to be sure that the medication is being taken as prescribed. Thus, this test should be used periodically in these long term studies to be certain that we do not falsely ascribe benefits to a drug which the patient may not be taking.

PAS sodium, as used in our clinic,[2] appears to be far from the ideal drug for outpatient treatment of pulmonary tuberculosis. The side effects and the large number of pills (24 per day) make it difficult to be sure that the medication is being taken by the patient as prescribed. It would appear that some other form of PAS should be sought to minimize this problem.

SUMMARY

Sixty-one patients with pulmonary tuberculosis supposedly taking PAS sodium as one of their anti-microbial drugs were subjected to a urine PAS test and questioned by a clinic physician. Twenty-five negative urine reactors and four positive urine reactors admitted taking PAS intermittently, irregularly or not at all. In all persons on PAS drug regimens, periodic check of the urine using Standard Erlichs Reagent is important to determine whether or not the patient is taking his medication.

RESUMEN

Se sujetaron a reacciones en busca de PAS en la orina y a un interrogatorio clínico, sesenta y un enfermos que se suponía tomaban PAS sódico y una de las drogas antimicrobianas. Veinticinco reactores negativos en la orina al PAS y cuatro positivos, admitieron que tomaban el PAS intermitentemente, con irregularidad o no lo tomaban del todo. En todas las personas bajo régimen de PAS, el examen de la orina usando el reactivo estandar de Erlich, es importante para determinar si el enfermo está tomando el PAS o no.

RESUME

61 malades atteints de tuberculose pulmonaire, qui étaient considérés comme absorbant du P.A.S. en même temps que leurs médications antimicrobiennes, furent soumis á un test d'élimination urinaire du P.A.S. et questionnés par un médecin. 25 individus ayant réagi négativement au test urinaire et 4 ayant réagi positivement admirent qu'ils prenaient le P.A.S. d'une facon intermittente, irrégulièrement, ou pas du tout. Chez tous les individus soumis à des régimes comprenant le P.A.S. il est important de pratiquer des contrôles périodiques de l'urine, en utilisante le réactif standard d'Erlich pour déterminer si le malade absorbe ou non la médication.

ZUSAMMENFASSUNG

61 Kranke mit Lungentuberkulose, von denen man unterstellen konnte, dass sie Na-PAS als eines ihrer antimikrobiellen Medikamente einnahmen, wurden mittels eines PAS-Testes im Urin untersucht und durch den Stationsarzt befragt. 25 Kranke mit negativen Harnproben und 4 Kranke mit positiver Probe räumten ein, PAS nur intermittierend, unregelmässig oder überhaupt nicht einzunehmen. Es ist wesentlich, bei allen Kranken, die unter PAS-Behandlung stehen. periodische Urinproben vorzunehmen unter Benutzung des Erlich'schen Standard Reagens, um festzustellen, ob der Patient seine Medizin auch einnimmt oder nicht.

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The Incidence of Pulmonary Tumors in Mice Exposed to Aerosols of Therapeutic Agents*

An Evaluation of the Possible Carcinogenic Properties of Penicillin, Pyribenzamine, Adrenalin, Cortisone, Trypsin and Desoxyribonuclease

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The Problem of Pulmonary Carcinoma:

In the early part of this century Adler surveyed the literature and found less than 400 recorded cases of primary cancer of the lung. During the ensuing 50 years the incidence of this condition has risen sharply, until now it is one of the most common causes of death in the male. Because of the steadily increasing mortality from this disease, carcinoma of the lung has become one of the most important problems in oncologic research.

Spontaneous Pulmonary Tumors in the Mouse:

The induction of pulmonary tumors in animals has become an acceptable experimental method of investigating agents that might prove carcinogenic and hence be hazardous to man. Selection of suitable animals for such studies has been difficult in the past, since spontaneous tumors of the lung are rare in most species. The establishment by Strong, in 1921, of an inbred strain of albino mouse (Strain A) which shows a high incidence of spontaneous lung tumors has greatly aided subsequent investigations. Bittner, in 1939, studied the range of occurrence of such tumors in strain A mice and found it to be highly predictable. The known incidence of tumors in the strain A mouse has been of great value in the *in vivo* testing of possible carcinogens.

Origin of Spontaneous Adenomatous Tumor in the Mouse:

The most common form of spontaneous tumor in the mouse, particularly strain A mice, is an adenoma, which can be readily induced with various hydrocarbons. This adenoma was first described by Livingood in 1896,[11] when he discovered spontaneous tumors in mice.

Opinions concerning the site of origin of the adenomatous tumor in mice varied among the early investigators. An extensive investigation by Mostafi and Larsen in 1951[12] showed that the induced pulmonary tumors originated from alveolar cells. They suggested that the discrepancy in opinions concerning the origin of the induced adenomatous tumor and its early development could be attributed to misinterpretation of the dilation of bronchioles and proliferation of the bronchiole cells that are occasionally found in areas of pneumonitis in mouse lungs.

Experimental Induction of Pulmonary Tumors in the Mouse:

The induction of pulmonary tumors in mice by means of chemical agents was first reported by Murphy and Sturm in 1925.[13] Using repeated cutan-

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eous applications of coal-tar distillate, these authors successfully induced adenoma identical with those that appeared spontaneously. Since that time investigators have used a number of other compounds, including nitrogen mustard, urethan, sulphur mustard, and several hydrocarbons, to induce pulmonary tumors in mice, especially in strain A animals.[2, 4, 7, 12-14]

In addition, a squamous cell carcinoma was induced by Andervont by inserting silk thread impregnated with 1, 2, 5, 6-dibenzanthracene directly into the lung.[1]

It is unfortunate that the squamous cell carcinoma described above was not identical with that found in man, since it would have served as a good experimental source of information on the commonest type of carcinoma of the lung in the human. In addition, because the type of tissue response to a chemical agent is often species specific, a drug that produces an adenoma or adenocarcinoma in the mouse may produce an entirely different neoplasm in man.

Despite these differences, studies of pulmonary tumors in strain A mice can provide much data concerning the mechanisms of tumor behavior and origin, some of which may be applicable to man. Certainly any drug found to have carcinogenic effects in animals should be used cautiously in the treatment of pulmonary diseases in the human.

Present Experimental Study

Purpose:

The purpose of this study was to investigate the possible carcinogenic effects in strain A mice of six drugs used in the treatment of pulmonary diseases. Penicillin, pyribenzamine, adrenalin, and cortisone were selected for study, since minimal information has been obtained in the past concerning their possible carcinogenic properties. Trypsin and desoxyribonuclease were also investigated for carcinogenic properties because of recent evidence of cytological changes in the sputum of patients undergoing treatment by inhalation of these two pancreatic enzymes.[6]

Materials and Methods:

Male and female strain A mice, 8 to 10 weeks of age, were employed in this experiment. All the drugs tested were given by inhalation. Aerosol preparations of the drugs were administered with a National Cylinder Gas humidifier-nebulizer under oxygen pressure that delivers an extremely dry spray of freely dispersed droplets of 4 micra in diameter or less. Periods of inhalation were carried out for three hours, five days a week, over periods of 10 to 23 weeks.

Series I Mice. Administration of Penicillin, Pyribenzamine, Adrenalin and Cortisone:

Six groups of mice, each consisting of 90 animals, were used in this study. The vehicle employed in administration of the drugs was 50 ml. of 5 per cent glycerol. The first group of mice received 20,000 units of penicillin (1 ml.), the second received 2.5 ml. of a 2 per cent solution of pyribenzamine, the third received 0.2 ml. of a 2.5 per cent solution of adrenalin, and the fourth received 10 mg. of cortisone. The fifth group, consisting of control animals, received no treatment. The sixth group was given the glycerol vehicle only. The mice in these two control groups were housed and fed in the same manner as the test animals.

The animals were treated for 10 weeks, and then allowed to live without further treatment until six months old.

Series II Mice. Administration of Trypsin and Desoxyribonuclease:

A total of 360 mice was employed in this series. The dose of trypsin was 250 mg. (250,000 units) in 100 ml. of phosphate buffer solution with a pH of 7.4, considered the optimum pH range for the enzymatic activity of trypsin; the dose of desoxyribonuclease was 200,000 units in 75 ml. of physiological saline. The control animals received no treatment and were maintained under the same diet and housing conditions as the treated animals.

The 360 mice in Series II were treated as follows: 50 animals received trypsin for 10 weeks and were sacrificed at six months of age; 50 animals received trypsin for 23 weeks and were sacrificed at nine months of age. Seventy animals were given desoxyribonuclease for 10 weeks and were sacrificed when six months old. Seventy animals were given desoxyribonuclease for 23 weeks and were sacrificed when nine months old. The 50 animals comprising the control group were sacrificed at six months of age; the remaining 70 control animals were sacrificed when nine months old.

All the animals in both series were sacrificed by cervical dislocation, and autopsies were performed immediately. The heart and lungs were removed *in toto* and fixed in formalin or Zenker-formalin. Histologic sections were prepared and stained with hematoxylin and eosin or with a modified Papanicolaou stain of hematoxylin, eosin-azure, and orange G.

The tumors were counted grossly, and the location of each was noted. Microscopically, the tumors were examined as to type, location and associated pathological processes such as atelectasis and pneumonitis. The number of tumors per animal and the percentage of tumors in each group were noted.

Results

Series I Mice. Effects of Penicillin, Pyribenzamine, Adrenalin and Cortisone:

The animals were sacrificed at six months of age following 10 weeks of treatment with one of the four drugs. A total of 113 tumors was found

TABLE I

LOCATION OF TUMORS FOUND IN THE LUNGS OF 6-MONTH-OLD MICE GIVEN PENICILLIN, PYRIBENZAMINE, ADRENALIN, OR CORTISONE FOR 10 WEEKS

		Lobes									
		Left		Right Upper		Right Middle		Right Lower		Lingula	
Drug	No. of Animals	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
Control-Untreated	90	5	35.7	2	14.3	2	14.3	3	21.4	2	14.3
Control-Glycerol Vehicle	90	10	52.7	5	26.3	2	10.5	0	0	2	10.5
Penicillin	90	5	27.8	3	16.7	4	22.2	2	11.1	4	22.2
Pyribenzamine	90	9	47.4	4	21.0	3	15.8	3	15.8	0	0
Adrenalin	90	6	31.6	5	26.3	5	26.3	1	5.3	2	10.5
Cortisone	90	9	37.5	3	12.5	3	12.5	7	29.1	2	8.4

in the 540 mice in this series. The reported incidence of spontaneous tumors in strain A mice at six months of age is 17 per cent.[10] In our series the incidence ranged from 14 per cent in the untreated mice to 26 per cent in the animals treated with cortisone. Analysis by the chi square method showed the percentage of tumors in the mice treated with cortisone to be statistically significant. The incidence of tumors in the animals treated with the other drugs was within the normal range. The average number of tumors per animal was 1.1, with the exception of the mice treated with cortisone which averaged 1.0 tumor each. The majority of tumors occurred in the left lung, and the smallest number in the lingula (Table I). The details of treatment and the results are tabulated in Table II.

Series II Mice. Effects of Trypsin and Desoxyribonuclease:

Ten tumors occurred in the 50 animals treated with trypsin for 10 weeks and sacrificed at six months of age, an incidence of 18 per cent. In the 50 mice treated with trypsin for 23 weeks and sacrificed at nine months of age, a total of 19 tumors was found, an incidence of 30 per cent. The reported incidence of spontaneous tumors in strain A mice at this age is 34 per cent.[15]

Twenty-seven tumors, an average of 1.3 tumor per animal, occurred in the 70 animals given desoxyribonuclease for 10 weeks and sacrificed at six months of age. The incidence of tumor in this group was 30 per cent, which is significantly greater than the reported incidence of 17 per cent of spontaneous tumors in six-month-old strain A mice.[10] In the 70 mice treated with desoxyribonuclease for 23 weeks and sacrificed at nine months of age, 40 tumors were found, giving an incidence of 46 per cent. This per-

TABLE II
INCIDENCE OF TUMORS IN STRAIN A MICE AFTER ADMINISTRATION OF TEST DRUGS

Drug	Animals No.	Animals Age	Duration of Treatment	No. of Mice with Tumors	Total No. of Tumors	No. of Tumors per Animal	Per Cent Animals with Tumors*
Series I							
Control-Untreated	90	6 months	10 weeks	13	14	1.1	14
Control-Glycerol Vehicle	90	6 months	10 weeks	17	19	1.1	19
Penicillin	90	6 months	10 weeks	16	18	1.1	18
Pyribenzamine	90	6 months	10 weeks	17	19	1.1	19
Adrenalin	90	6 months	10 weeks	18	19	1.1	20
Cortisone	90	6 months	10 weeks	23	24	1.0	26
Series II							
Control-Untreated	50	6 months	10 weeks	21	22	1.1	21
	70	9 months	23 weeks	40	57	1.4	40
Trypsin	50	6 months	10 weeks	9	10	1.1	18
	50	9 months	23 weeks	15	19	1.3	30
Desoxyribonuclease	70	6 months	10 weeks	21	27	1.3	30
	70	9 months	23 weeks	32	40	1.3	46

*The reported incidence of spontaneous tumors in strain A mice at six months of age is 17 per cent[10] and at 9 months of age is 34 per cent.[15]

centage, although above the reported normal incidence in nine-month-old mice, is proportionately less than the increase found in the six-month-old mice. The details of treatment and results are given in Table II.

Gross and Microscopic Appearance of Tumors:

Macroscopic and microscopic examination revealed no significant differences in the lungs of the experimental animals in all groups. The pulmonary tumor found in all the animals was the typical adenoma which occurs frequently in strain A mice. Grossly, the tumor was firm, pearly white, about 1 to 2 mm. in diameter, and usually located in the periphery of the lung tissue.

FIG. 1

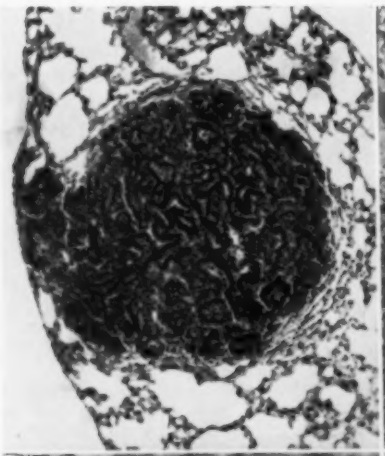

FIG. 2

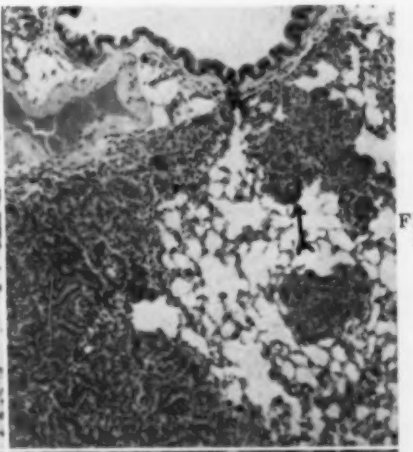

FIG. 3

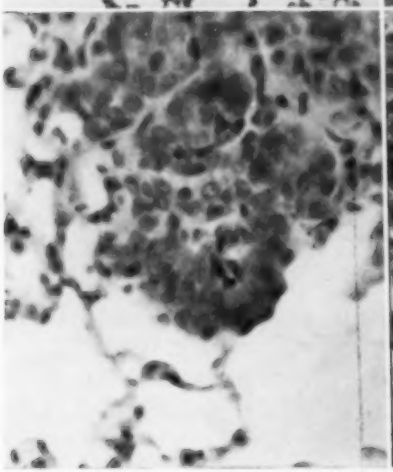

FIG. 4

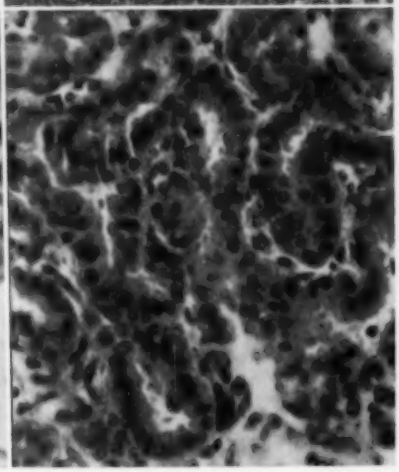

Figure 1: The pulmonary tumor found frequently in the strain A mice. Note its location in the periphery of the parenchyma, lack of relationship to bronchioles and bronchi and absence of encapsulation, and its typical papillary-acinar pattern (X 240).—*Figure 2:* Areas of tumor arising near a bronchus. A higher magnification of the area of tumor marked "A" is shown in Figure 3 (X 480).—*Figure 3:* A higher magnification of the area marked "A" in Figure 2. Note the normal alveolar walls near the tumor (X 2880).—*Figure 4:* Higher magnification of a characteristic area in the tumor in Figure 1 showing the papillary-acinar structure formed of cuboidal epithelial cells intermixed with occasional columnar cells (X 2880).

Microscopically, the tumor was well circumscribed in most instances, but lacked a definite capsule (Figure 1). In several instances the compressed parenchyma in the proximal portion of the tumor formed a pseudocapsule. Only four tumors were found near a major bronchus (Figures 2, 3); the majority of tumors showed no immediate relationship to the terminal and respiratory bronchioles. In those tumors that did show a definite relationship to a respiratory bronchiole, however, the morphological changes in the cells were evident (Figures 2 and 3). The tumor cells appeared to adhere to the alveolar framework, especially in the early-developing tumors.

The tumor cells were arranged in the typical papillary-acinar structure (Figure 4), and were fairly uniform in size, shape, and staining properties. The cytoplasm was acidophilic, and the nuclei were similar in size and shape. The chromatin pattern was evenly distributed, and the nucleoli were not prominent. There was minimal hyperchromatism, and mitotic figures were rarely seen. The cell type was cuboidal, although in most areas a few tumor cells which were columnar in character could be seen.

DISCUSSION

Postulation of Etiology of Tumor:

A specific explanation for the increased incidence of tumors in the animals treated with either cortisone or desoxyribonuclease cannot be offered at this time, but certain factors may be postulated to serve as a guide for future studies. The viral etiology of tumor development has been proposed in the past, and studies showing that the growth potential of tissue is influenced by the presence of viruses have been reported. For instance, Steiner and Loosli have described the powerful stimulus of the human (Type A) influenza virus on the growth of bronchial epithelium in the mouse.[26] Other investigators have demonstrated that a specific virus will induce breast carcinoma in mice if two prerequisites are met: a specific strain of mice with hereditary susceptibility, and the experimental administration of estrogen.[5] In like manner, desoxyribonuclease, or cortisone, may act as a co-carcinogen and influence the development of a virus-induced pulmonary adenoma in the strain A mouse.

The carcinogenic action of desoxyribonuclease, and to a lesser degree, cortisone, in this series is of particular interest. The presence of an initial "trigger" action is indicated by the significant increase in tumors in animals treated for 10 weeks and sacrificed at 6 months of age. The incidence of tumors in the mice treated with desoxyribonuclease for 23 weeks and sacrificed at nine months of age, although increased, was not significant. Conversely, the action of trypsin appears to be inhibitory, as evidenced by the low incidence of tumors in the 9-month-old animals compared to the controls. Although both these pancreatic enzymes are mucolytic in action, desoxyribonuclease apparently has an inherent carcinogenic property not possessed by trypsin.

The absence of carcinogenic effects after administration of adrenalin and of glycerol, the vehicle used for administration of the test drugs, confirms the previous work of Bauer,[3] Holck,[8] and Johnson.[9]

Microscopic Evaluations:

The tumors which developed in the experimental animals in this series were typical of the adenoma found in strain A mice. In general, the histologic appearance of the tumors suggested that they originated from alveolar cells. A very limited number of specimens, however, showed close relationships to bronchioles, although the cell types were dissimilar.

The anatomical distribution of the tumors in our series of animals, with the largest number in the large left lobe of the lung and the smallest number in the lingula, suggests that the site of tumor development is related to the quantity of lung parenchyma present and not to any specific growth potential inherent in a particular area of lung tissue.

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SUMMARY

1. The steadily rising incidence of cancer of the lung indicates that any drug found to have carcinogenic effects in animals should be used with caution in the treatment of pulmonary disease in man. The present investigation was undertaken to determine

possible carcinogenic properties of therapeutic agents, as evidenced by the development of pulmonary tumors in mice.

2. Penicillin, pyribenzamine, adrenalin, cortisone, trypsin, and desoxyribonuclease were administered by aerosol inhalation to groups of mice. Strain A mice were used because of the reliable incidence of spontaneous pulmonary tumors in this strain. Treatment was carried out over 10 to 23 week periods; the animals were sacrificed at six and nine months of age.

3. The tumors that developed in all groups were typical of the adenoma that occurs spontaneously in strain A mice. The histologic appearance of the tumors suggested that they originated from the alveoli.

4. The animals treated with cortisone and with desoxyribonuclease for 10 weeks and sacrificed at six months of age showed a statistically significant increase in tumors. The incidence was 26 per cent and 30 per cent, respectively, whereas the reported incidence of spontaneous tumors in 6-month-old strain A mice is 17 per cent. The action of trypsin appeared to be inhibitory, as evidenced by the lower than normal incidence of tumors in the 9-month-old animals treated with this agent. The occurrence of tumors in the animals given the other test drugs was within the normal range.

5. Although no definite conclusion can be drawn at this time, it is postulated that desoxyribonuclease and cortisone may act as co-carcinogens and influence the development of a viral-induced pulmonary adenoma in the strain A mouse.

RESUME

1. Etant donné la fréquence constamment croissante du cancer du poumon, tout produit réputé avoir des effects carcinogènes sur les animaux ne devrait être utilisé qu'avec prudence dans le traitement des affections pulmonaires de l'homme. La présente étude fut entreprise pour déterminer les propriétés éventuellement carcinogènes des agents thérapeutiques. On utilisa dans ce but la détermination sous leur action de tumeurs pulmonaires chez la souris.

2. La pénicilline, la pyribenzamine, l'adrénaline, la cortisone, la trypsine et la désoxyribonucléase furent administrées par inhalation en aérosols à des lots de souris. On utilisa la souche A de souris à cause de la fréquence des tumeurs pulmonaires qui frappent spontanément ce groupe. Le traitement fut poursuivi pendant 10 à 23 semaines; les animaux sacrifiés étaient âgés de six à neuf mois.

3. Les tumeurs qui se développèrent dans tous les lots curent les caractères typiques de l'adénome qui survient spontanément dans la souche A de souris. L'aspect histologique des tumeurs permettait de penser qu'elles étaient d'origine alvéolaire.

4. Les animaux traités par la cortisone, et la désoxyribonucléase pendant dix semaines, et sacrifiés à l'âge de six mois, montrèrent une augmentation statistiquement importante des tumeurs. La fréquence fut de 26 et de 30% respectivement, tandis que la fréquence des tumeurs spontanées chez les souris de la souche A âgées de six mois est de 17%. L'action de la trypsine sembla inhibitrice comme l'a mis en évidence la fréquence au-dessous de la normale des tumeurs chez les animaux âgés de 9 mois traités par ce produit.

La fréquence des tumeurs chez les animaux soumis aux autres produits fut comprise dans la limite normale.

5. Bien qu'aucune conclusion précise ne puisse être tirée en ce moment, l'auteur suggère que la désoxyribonucléase et la cortisone peuvent agir comme co-carcinogènes et influencer le développement d'un adénome pulmonaire d'origine viral chez les souris de la souche A.

RESUMEN

1. El aumento constante de la frecuencia del cáncer del pulmón indica que cualquier droga que se descubra que tenga efecto carcinogénico en los animales, debe usarse con precauciones en el hombre al tratarse enfermedades pulmonares. Esta investigación se emprendió para determinar las posibilidades carcinogénicas de agentes terapéuticos tal como puede hacerse evidente por el desarrollo de tumores pulmonares en ratones.

2. Se administraron por aerosol, penicilina, piribenzamina, adrenalina, cortisona, tripsina y desoxiribonicleasa en un grupo de ratones. Se usó la cepa de ratones A porque en ellos es de esperarse el desarrollo de tumores espontáneos del pulmón. Se prolongó el tratamiento de 10 a 23 semanas; los animales se sacrificaron a los seis y a los nueve meses de edad.

3. Los tumores que se desarrollaron en todos los grupos eran típicos adenomas que se ven espontáneamente en la cepa A de ratones. La apariencia histológica sugiere que se originaron en los alveolos.

4. Los animales tratados con cortisona, y con desoxiribonucleasa por diez semanas y sacrificados a los seis meses de edad mostraron un aumento, de los tumores de significación estadística. La incidencia fué de 26 y 30 por ciento respectivamente en tanto que la incidencia espontánea a los seis meses en esa cepa es de 17 por ciento. La acción de la tripsina parece ser inhibitoria como evidencia la incidencia menor que la normal en los animales tratados con esa substancia. La incidencia en el resto de los animales tratados con las otras drogas mencionadas, fué normal.

5. Aunque no se pueden extraer conclusiones definidas por ahora, se supone que la desoxiribonucleasa y la cortisona pueden actuar como co-carcinogénicos y así influir el desarrollo del adenoma pulmonar producido por virus en la cepa A de ratones.

ZUSAMMENFASSUNG

1. Das ständig zunehmende Vorkommen von Lungenkrebs weist darauf hin, dass jedes Medikament, von dem sich herausgestellt, dass es carzinogen Eigenschaften bei Tieren hat, mit Vorsicht bei der Behandlung pulmonaler Krankheiten des Menschen gebraucht werden sollte. Die vorliegende Untersuchung wurde unternommen, um die möglichen carzinogenen Eigenschaften tharapeutischer Stoffe zu bestimmen, wie sie sich durch die Entwicklung von Lungentumoren bei Mäusen zeigen.

2. Penicillin, Pyribenzamin, Adrenalin, Cortison, Trypsin und Desoxyribenuclease wurden Gruppen von Mäusen durch Aerosol-Inhalationen verabfolgt. Der Mäusestamm A wurde benutzt wegen der zuverlässigen Häufigkeit von spontanen Lungentumoren bei diesem Stamm. Die Behandlung wurde über 10-23 Wochen-Perioden durchgeführt; die Tiere wurden mit einem Alter von 6 und 9 Monaten getötet.

3. Die Tumoren, die sich in allen Gruppen entwickelten, waren vom Typ des Adenoms, wie es spontan im Mäusestamm A auftritt. Das histologische Aussehen der Tumoren lässt vermuten, dass sie von den Alveolen abstammen.

4. Die 10 Wochen mit Cortison und mit Desoxyribonuclease behandelten und im Alter von 6 Monaten getöteten Tiere zeigten eine statistisch signifikante Zunahme der Tumoren. Die Häufigkeit lag bei 26% bzw. 30%, während die mitgeteilte Häufigkeit von Spontantumoren bei 6 Monate alten Mäusen vom Stamme A 17% betrug. Die Wirkung von Trypsin schien eine hemmende zu sein, wie sich ergab aus dem geringeren als normalen Vorkommen von Tumoren unter den 9 Monate alten Tieren, die mit diesem Stoff behandelt waren. Die Tumorhäufigkeit unter den Tieren, die andere Stoffproben erhalten hatten, lag innerhalb der normalen Werte.

5. Obwohl zur Zeit noch keine definitive Schlussfolgerung gezogen werden kann, wird die Forderung erhoben, dass Desoxyribonuclease und Cortison als co-carzinogene Substanzen wirken können und die Entwicklung eines virus-induzierten pulmonalen Adenoms im Mäusestamm A beeinflusst.

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The Tuberculin Test — a Tool in Case Finding*

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It was about 30 years ago, in May, 1927, that the Wisconsin Anti-Tuberculosis Association carried on its first tuberculin testing studies. Sixty-eight boys and 130 girls in three Wisconsin child-caring institutions—or orphanages, as we called them then—were given von Pirquet tests. In July of the same year, 270 children at the State Public School for Dependent Children at Sparta were similarly tested.

Among these 468 children, a reaction rate of 20.5 per cent was found. This was, for the time and place, an almost revolutionary finding, for the generally held opinion among physicians and public health workers was that, as Naegeli reported from autopsies in 1900, "everybody had a little tuberculosis." It was widely believed that reaction rates among children, and particularly those orphaned, would be well nigh universal.

There is no record of more tuberculin testing by the Wisconsin Anti-Tuberculosis Association until 1931, when approximately 4,000 children and young adults, mostly in school situations, were tested intradermally with various strengths of old tuberculin. Among these 3,975 individuals, 25.9 per cent reacted.

The Wisconsin Anti-Tuberculosis Association (WATA) did not then have—nor did it have for many years afterward—x-ray or fluoroscopic examining equipment to follow up on reactors. It did, however, make an earnest effort to obtain medical follow-up through health departments and physicians' offices.

It is therefore impossible to report how many cases of active tuberculosis were found among these reactors. But the values of the tuberculin test quickly impressed themselves upon the medical staff of the WATA. Writing in the monthly publication of the Association, The Crusader, a staff physician, Dr. Florence E. MacInnis, thus listed the WATA's aims in conducting tuberculin testing programs:

1. To find those who have been infected.
2. To find among the infected those who have tuberculous disease.
3. To refer those who have tuberculous disease to the family physician for further observation and study to determine if the disease is active.
4. To assist in procuring proper care for those ill with tuberculosis.
5. To educate the reactors to the necessity of repeated examinations and observation by their physician for years to come.

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6. To aid in formulating individual programs for those reactors who are likely to break down with tuberculous disease if they do not lead a well regulated life.

7. To point the way to possible sources of infection. Each member of the family and household of a reactor should be tuberculin tested and if positive, examined, x-rayed and given such other study as is indicated. This, because the disease is frequently spread in deadly forms by individuals with so mild a form that they and their families have never even suspected its existence.

8. To impress upon those who are negative to tuberculin the necessity of retests at yearly intervals in order that they may know when infection may have occurred.

It is interesting that no mention is made in this listing of three values of the test widely recognized today: as a tool of differential diagnosis, as a statistical measurement of infection rates—and hence of relative morbidity of various population groups—and as a peg upon which to develop community educational programs.

In closing, Dr. MacInnis wrote thus:

"This program has just begun. We shall have to repeat and repeat and repeat its aims and accomplishments before its roots become firmly implanted."[1]

That was a quarter of a century ago. Through all these years the Wisconsin Anti-Tuberculosis Association has preached and practiced tuberculin skin testing. Through the rising tide of popularity of the test in the 1930's, the unfashionableness of the test in the 1940's (when mass x-raying was the overwhelming case-finding tool of choice), and now again in the 1950's when the tuberculin test appears to be winning back its friends—through all these years, the WATA has continued to repeat and repeat and repeat the *aims* of the tuberculin test.

In recent years it has seemed desirable to the Association to try to evaluate the *accomplishments* of the test in two areas where they presumably can be measured: in helping to find cases among reactors, and in pointing the way to probable sources of infection.

Five years ago, three members of the staff of the Wisconsin Anti-Tuberculosis Association studied tuberculin testing programs reported to have been carried on through Wisconsin public health nursing services. Questionnaires sent to 65 such departments revealed that 49 nursing services had school tuberculin testing programs during the year 1950 that could properly be included, and that through these 49 services, 45,804 individuals were so tested. In the report on the study, it was concluded that this total included "approximately three-fourths of all tuberculin testing carried on in the state during the year."[2]

These 45,804 individuals included 9,582 who were adults, or individuals on whom reaction or age classification was unknown. Omitting them, there were something over 36,000 individuals of ages one to 18 on whom reaction rates could be computed.

Recently, a similar study of school groups was done for the year 1955. Through the Tuberculosis Division of the Wisconsin State Board of Health, inquiries were made of public health nursing services all over the state.

These inquiries revealed that some 38,270 tuberculin skin tests were known to have been given through public health nursing services during 1955. Again omitting adults and individuals of unknown age, we have 32,975 persons of ages one to 19 who are known to have been tested.

Doubtless, some programs were missed in this study also. There are also certain differences between the two surveys; in the first, for example, the top age included was 18 years, in the second, 19 years.[3]

But a comparison of findings in the two surveys provides some interesting and perhaps significant observations.

The first observation may be made from Figure 1.

In spite of all the "repeat and repeat and repeat" in Wisconsin over the last 25 years on the value of the tuberculin skin test, we have evidence that only one child in 27 appears to have had a tuberculin test in 1950. The ratio had not risen by 1955. In fact, considering the marked proportional increase in the "under 19" age group, with the post-war boom in babies, it appears to have declined to about one in 37. Even if we arbitrarily assume that these studies include only about 75 per cent of persons tested, we may surmise that only one child in 19 was tested in 1950 and one in 26 in 1955.

The second observation may be made from Figure 2.

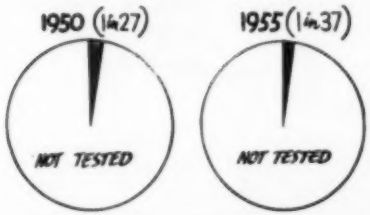
Among the 36,222 persons tested in 1950, who are known to have been 18 or under, there were 1,786 (5.0 per cent) reactors. Among the 32,975 individuals of 19 or under known to have been tested in 1955, there were 849 (2.6 per cent) reactors.

Since the age distribution in the two surveys was roughly comparable, there appears, then, to have been a substantial drop in the infection rate from 1950 to 1955.

This marked drop in reaction rates is corroborated in a sense in Figure 3, which gives findings of active disease for the two years.

Among the 36,222 children known to have been tested in 1950, there were 18 active cases found. Among the 32,975 tested during 1955, there were 6 active cases found. (Actually, one of these cases may have been a false alarm.) Or, as we see from figure 3, there was one active case found among 2,000 children tested in 1950; one case among 5,600 children tested during 1955.

There thus appears to be a tremendous drop in prevalence of active tuberculosis among children of school and pre-school age. Yet too much



POPULATION of WISCONSIN, 19 and UNDER, KNOWN TO HAVE BEEN TUBERCULIN TESTED

Fig. 1

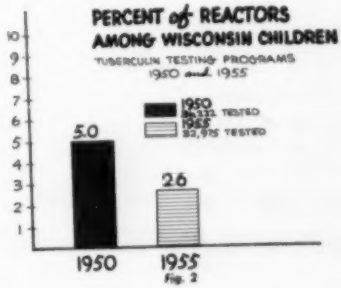


Fig. 2

should not be read into these figures. For one thing, the completeness of follow-up is unknown; 1955 was a year when public health nurses in Wisconsin were concentrating on polio vaccination programs, and tuberculosis control may have had to be by-passed to some extent. For another, the numbers involved are small.

To illustrate how a single situation may radically alter the picture, we can jump ahead to 1956, when an actively tuberculous teacher taught out her school year in a rural district in southern Wisconsin because her disease was unrecognized until she returned home to another county for the summer vacation. Fast and effective work by an alert health service of the first county, when informed of the teacher's disease, led to the discovery that 30 of the 33 children in her school were tuberculin positive. Six children of school age, or of preschool age in the home where the teacher boarded, were subsequently admitted to a Wisconsin sanatorium.

Had this particular school been tuberculin tested late in 1955 rather than in the summer of 1956, markedly higher findings for the year might have been reported.

To see the findings by stage of disease among the cases reported for 1950 and 1955, we may compare them in Figure 4. In the former group of 18 cases, 14 were in the minimal or primary stages; only 4 were moderately advanced and none was far advanced. In the latter group of 6 cases, five were in the primary or minimal stages, one case was of undetermined degree, and there was no advanced case.

The conclusion which might be drawn from these figures is that tuberculin testing uncovers but few clinical cases among younger age groups, and that its use as a case-finding tool in this population is therefore economically unjustified. This, however, would be like adding two and two together and getting five.

It is quite true that tuberculin testing programs uncover few clinical cases among school children. The reason is simple: there are relatively few cases of TB to be found among school children. But if we agree that finding these cases among school children—and finding them early—is highly desirable, then we have two alternatives: tuberculin testing all school children and x-raying the reactors, or by-passing the tuberculin test and x-raying all school children.

Today, with continually lowering infection rates and the costliness of x-raying large population groups, we can hardly justify the latter proce-

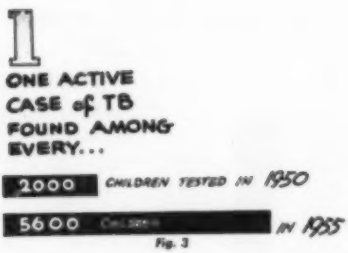
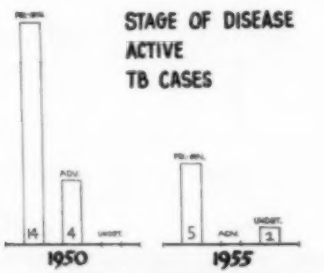


Fig. 3



FOUND AMONG WISCONSIN CHILDREN THROUGH TUBERCULIN TESTING PROGRAMS
Fig. 4

dure on a case discovery cost basis. While we can still defend x-raying of susceptible or vulnerable groups, it is becoming more difficult to vindicate the idea of chest films for all. It seems more practical to educate and skin test. We can then go on more economically with other phases of our case discovery program, including chest films, search for tubercle bacilli, etc. Early treatment and ultimate control of tuberculosis can thus be accomplished most economically.

We may now go on to a second value of tuberculin skin testing programs among younger age groups—this time not as a clue in uncovering TB among the children themselves, but as a clue in uncovering TB among the adults in their homes.

Figure 5 shows findings among associates of reactors. In 1950 there were 7 active cases reported among these associates, four of whom were in an advanced stage. In 1955, there were four active cases reported among these associates, two of whom were advanced.

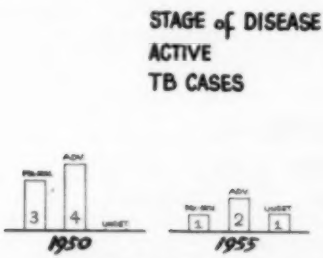
No conclusions should be drawn from these meager findings except the pretty obvious one that cases found among associates of reactors are likely to be more advanced than the cases seeded by them among their children or child associates.

The reason for this caution is brought out in Figure 6. Here we see the number of reactors and the number of contacts examined per five-year age group in 21 nursing services reporting on this matter for 1955. There is a sharp plunge downward in the ratio of contacts examined to reactors as we move from reactors who are infants to reactors who are of grade and high school age. Certainly the number of family associates does not decrease so rapidly. It would appear that parents and other associates of older child reactors are not as easily persuaded to be x-rayed.

It thus appears that the second value of the tuberculin test as a clue in case-finding is not nearly as well grasped as the first.

Figure 7 brings out in capsule form the conclusion which is suggested by several of the preceding figures. There was apparently a marked drop in the number of tuberculin tests carried on in organized programs from 1953 to 1954, and another marked drop from 1955 to 1956.

Reference was made early in this paper to the fact that the differential diagnosis, social research and educational values of the tuberculin skin test were not clearly seen in the early years of tuberculin testing programs. Later in the paper, reference was made to an episode in southern Wiscon-



FOUND AMONG ASSOCIATES OF REACTORS IN TUBERCULIN TESTING PROGRAMS AMONG WISCONSIN CHILDREN

Fig. 5

Age Group	No. Reactors	No. Contacts Examined	No. Contacts Examined Per Reactor
Under 1 year	3	16	5.3
1-4	10	42	4.2
5-9	141	243	1.7
10-14	260	278	1.1
15-19	237	203	.9

CONTACTS EXAMINED, TUBERCULIN TESTING PROGRAMS AMONG WISCONSIN CHILDREN, 1955

Fig. 6

sin in the summer of 1956 when 30 of 33 school children exposed to an actively tuberculous teacher were found to be tuberculin reactors and how at least six of the school and pre-school children exposed to her have since entered a Wisconsin sanatorium.

This is not the time or place to discuss the social research or differential diagnosis values of the tuberculin skin test. With respect to the first, it becomes increasingly clear that there is a wide variation in tuberculin reaction rates in specific groups of the population, and that these reaction rates point to higher morbidity rates. With respect to the second, it is also increasingly clear that the tuberculin skin test is an extremely useful tool in deciding whether suspicious x-ray or laboratory findings are due to tuberculosis; thus, a negative response to the test washes out the significance of many symptoms suggesting tuberculosis.

But a brief review may be in order of the educational values of the tuberculin skin test, particularly as they were exemplified in Wisconsin by the so-called "Fitchburg Case." It broke in the July 31, 1956 issue of Wisconsin's largest daily. Other papers about the state printed similar stories. Within a few weeks a tremendous chain of public reaction set in. Strong editorials demanded protection of school children. School systems set up voluntary programs for required x-raying of school employes.

County health committees and county boards of supervisors called upon their local members in the Wisconsin Legislature to introduce legislation for mandatory health examinations of school employes. The Wisconsin County Boards Association, a group with tremendous political influence, adopted quite voluntarily at its state meeting, a few weeks later, a call for legislation specifying "that all personnel connected with the schools be required to submit to a physical examination and a chest x-ray film or such other test that may be required for the determination of whether or not such person is an active tuberculosis case."

The Wisconsin Congress of Parents and Teachers took similar action at its state meeting. So, too, did the Wisconsin Welfare Council. So, too, did the Division of Tuberculosis and Diseases of the Chest of the State Medical Society.

Instead of one bill, five bills were introduced, and with many sponsors. Working closely together, the State Medical Society, State Board of Health, and the Wisconsin Anti-Tuberculosis Association ironed out minor differences in points of view. The final draft of the bill, as enacted into law, provided for tuberculosis check-ups of all school personnel (excluding those objecting on religious grounds), at public expense, before employment and every three years thereafter, and including either a chest x-ray film or a tuberculin test, followed by a chest x-ray film if the skin test is positive.

WISCONSIN PERSONS TUBERCULIN TESTED IN YEARS 1953-55
ACCORDING TO STATE BOARD OF HEALTH
Fig. 7

A year before, no one dreamed of such a development. Such is the power of public education arising from the dramatic consequences of a single schoolroom situation.

SUMMARY

1. It would appear that we cannot build a good case for school tuberculin testing programs on the basis alone of active clinical cases among the school populations studied. The "yield" is low compared with case-finding programs in certain other groups in the population—and appears to be declining rapidly.

2. Cases found through such studies, however, are early. They are also found more economically than through general x-raying of school populations.

3. Follow-up of family associates of child reactors, while an excellent idea in theory, is as yet spotty in practice.

4. Just as 25 years ago, we must "repeat and repeat and repeat" if tuberculin testing programs are to go forward in quantity and quality. Without such eternal emphasis and re-emphasis, they are likely to stagnate.

5. The educational impact of the tuberculin skin test, and of cases found through it, may in the end be the greatest value of the test. The skin test, like the chest x-ray film and other screening tests, must be valued by the part it plays in the total tuberculosis control program—not by the dollar sign. In the words of a famous victim of tuberculosis, Robert Louis Stevenson, writing in one of his delightful books of travel, "The most beautiful adventures are not always those we go to seek."

RESUMEN

1. Parecería que no podemos presentar una buena justificación para los planes de pruebas tuberculínicas escolares sobre la sola base de los casos clínicos activos entre los grupos escolares que estudiamos. El rendimiento es muy bajo comparado con los programas de búsqueda de casos en otros grupos determinados de la población y parece que rápidamente está declinando.

2. Los casos descubiertos por tales estudios son sin embargo, tempranos. Se encuentran con menos gastos que por los rayos X en los grupos escolares.

3. Aunque el seguimiento de los familiares de los niños reactores parece una idea excelente, en la práctica, tiene dificultades.

4. Como hace 25 años, debemos "repetir, y repetir y repetir" si se desea que las reacciones tuberculínicas progresen en cantidad y en calidad. Sin tal énfasis permanente y reiterado ellas tienden a estancarse.

5. La huella educativa de la prueba tuberculínica y de los casos encontrados por ella, puede ser al fin de gran valor para el método. La prueba cutánea como la de las películas de rayos X y otras pruebas de detección deben estimarse por la parte que desempeñan en el plan integral de lucha contra la tuberculosis, no por el valor en monedas de ella. Como decía una víctima famosa de la tuberculosis, Roberto Luis Stevenson, al escribir uno de sus deliciosos libros de viajes: "Las aventuras más bellas no son siempre aquéllas que buscamos."

RESUME

1. Il apparaitrait que nous ne pouvons établir une bonne base de programme d'étude des réactions tuberculiniques dans la population scolaire, sur la seule connaissance des cas cliniques actifs dans la population scolaire étudiée. Le "matériel" est de trop peu d'importance, comparé aux programmes de dépistage de certains autres groupes de la population, et semble diminuer rapidement.

2. Les cas dépistés grâce à de telles études sont cependant précoces. La méthode se montre également plus économique que la radiologie systématique des populations scolaires.

3. La surveillance de l'entourage familial des enfants réagissant à la tuberculine, bien qu'excellente en théorie, s'est trouvée assez limitée dans la pratique.

4. Depuis 25 ans, nous devons "répéter et répéter" que le dépistage à la tuberculine doit progresser en quantité et en qualité. Sans une telle éternelle insistance et reinsistance, il ne fait que stagner.

5. Le choc éducatif du test cutané tuberculinique et des cas qu'il permet de découvrir, peut finalement être la plus grande valeur du test. Le test cutané, comme le film thoracique, et autres tests radiologiques, peut être estimé selon le rôle qu'il joune dans l'ensemble des programmes de contrôle pour la tuberculose, non selon la valeur monétaire. Selon les mots d'une éminente victime de la tuberculose, Robert Louis Stevenson, écrivant dans un de ses délicieux livres de voyage, "les aventures les plus belles ne sont pas toujours celles que nous avons recherchées."

ZUSAMMENFASSUNG

1. Es hat den Anschein, dass wir keinen Aussicht auf Erfoig haben mit einem Tuberkulin-Proben-Plan für Schulen nur auf der Basis klinisch-aktiver Fälle bei den untersuchten Schulkindern. Der "Vertrag" ist sehr gering im Vergleich zu Plänen für Fallsuche unter gewissen anderen Gruppen der Bevölkerung; ausserdem scheint er in raschem Rückgang begriffen.

2. Es handelt sich bei durch solche Untersuchungen gefundenen Fällen allerdings um Frühreife. Ihre Auffinding ist auch wirtschaftlicher als mittels genereller Röntgenuntersuchung aller Schulkinder.

3. Nach Kontrolle bei Familienangehörigen von Kindern mit positiver Reaktion bleiben, obwohl in theoretischer Hinsicht eine ausgezeichnete Idee, trotzdem in der Praxis mangelhaft.

4. Ebenso wie vor 25 Jahren müssen wir "wiederholen und immer wieder wiederholen," wenn Pläne für Tuberkulinprüfungen an Quantität and Qualität gewinnen sollen. Ohne eine solche beständige Betonung und abermalige Betonung werden sie wahrscheinlich stagnieren.

5. Das erzieherische Zusammenwirken von Tuberkulinhautprobe und von dadurch gefundenen Krankheitsfällen mag am Ende der grösste Wert des Testes sein. Die Hautprobe muss gleich wie die Thoraxröntgenaufnahme und andere Suchmethoden taxiert werden nach ihrer Rolle, die sie im gesamten Tuberculosebekämpfungsplan spielt—nicht nach der Zahl der Dollars. Mit den Worten eines berühmten Opfers der Tuberkulose Robert Louis Stevenson aus seiner entzückenden Reisebeschreibung sind "die schönsten Abenteuer nicht immer diejenigen, die zu suchen wir ausziehen."

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3 From unpublished data furnished Wisconsin Anti-Tuberculosis Association by Mrs. Agnes Jensen, R.N., Public Health Nursing Consultant in Tuberculosis, Wisconsin State Board of Health. The authors are much indebted to Mrs. Jensen and to the public health nursing services of Wisconsin for the information and statistics upon which much of this paper is based.

The Place of Excisional Surgery in the Treatment of Pulmonary Mycotic Infections*

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and JAMES H. MATTHEWS, M.D., F.C.C.P.
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Resection of lung tissue has been carried out at this institution for various fungus infections of the lungs, including actinomycosis, aspergillosis, mucormycosis, and sporotrichosis. However, this discussion will be limited to a consideration of the role of excisional surgery in the management of patients who are infected with one of the three major fungus diseases of the lungs; namely North American blastomycosis, coccidioidomycosis, and histoplasmosis.

Excellent up-to-date reviews of various aspects of these three infections have recently been published,[1-8] These infections have in common a number of characteristics. All three manifest themselves in localized and disseminated forms. In all three, the principal portal of entry is the lung. In each, there is a strong roentgenographic resemblance, at times, to pulmonary tuberculosis, and indeed, in an appreciable proportion, ranging up to 20 per cent of cases, pulmonary tuberculosis may coexist with one or another of them. All three are certainly to be considered in the differential diagnosis of pulmonary diseases, be they nodular densities, chronic infiltrates, or cavitary lesions. All occur from exogenous sources or reservoirs and are endemic in certain fairly well-defined geographic areas. However, while the known endemic areas of each may be limited in extent, clinical cases may and do occur almost everywhere in the United States and elsewhere. This is probably due to the frequency and ease of travel in this country by such a large segment of the population, both civilian and military.

It has seemed to us that there is little unanimity of opinion among pathologists, mycologists, internists, and thoracic surgeons regarding the types of pulmonary lesions which might require surgical management. Also, since the total experience with these diseases is still somewhat limited, no clear idea emerged as to what can be expected of surgical therapy, as compared with medical treatment. Since we are seeing patients with all three types of mycotic infections with some regularity, these questions have prompted us to review our own experiences, and that of others, in an attempt to arrive at least at some approximate evaluation of the place of surgery in the treatment of these infections.

During the past 12 years, we have treated 75 patients with these three mycotic infections. Twenty had blastomycosis, and resections were carried out in seven. Twenty had coccidioidomycosis, and of these, 11 were subjected to resective surgery. Thirty-five with histoplasmosis were seen, of whom 10 had resection of lung tissue on which a histological or cultural diagnosis was made. The experience with these patients,

*From the Veterans Administration Hospital. Presented at the meeting of the Southern Chapter of the American College of Chest Physicians, Miami, Florida, November 10, 1957.

together with a survey of the available literature, constitutes the body of this report. Each group, presenting as it does, a distinctly different problem, will be treated separately.

I. Blastomycosis

In a previous report,[9] we detailed the results of treatment in 15 patients who were seen at Oteen with blastomycosis. Four had had pulmonary resections. Our experience now totals 20, in seven of whom diseased lung was resected.

Of the seven surgical patients, two died. One succumbed to disseminated blastomycosis six months after surgery while the second (who also had bronchogenic carcinoma and pulmonary tuberculosis, as well as pulmonary blastomycosis), died of pulmonary insufficiency. The five who survived resections are well clinically, but two have residual lesions and blastomyces dermatitidis in the sputum, in spite of intensive therapy with the aromatic diamidines. One of these has also been given amphotericin-B recently (see Table I).

Of the 13 who did not have resective lung surgery, three died: two with disseminated blastomycosis, and one (on whom no autopsy was performed) had proved cutaneous blastomycosis with pulmonary cavitation. This patient had sputum positive for acid fast bacilli and negative for blastomyces dermatitidis and it is not established whether his pulmonary disease was tuberculosis, blastomycosis, or both. Ten are living who did not have pulmonary resections. In five the disease is now apparently arrested, although one is still on drug therapy. Two refused treatment and left the hospital, and three still have active disease, as evidenced by finding organisms in the sputum or prostatic secretions.

Stilbamidine and/or 2-hydroxystilbamidine had been used in nine patients of the entire group of 20; undecylenic acid in 12; and amphotericin-B in three. Seven had more than one of these four drugs, and one received all four.

Having reviewed these results, we undertook a search of the recent available medical literature. Including our own patients, we were able to collect 47 cases of pulmonary resection for blastomycosis for analysis and review,[10-24] and 113 cases treated by administration of either stilbamidine or 2-hydroxystilbamidine or both.[25-53] Thirteen received both an aromatic diamidine and resective lung surgery.

Of the 47 on whom resections were carried out, 11 died, six apparently of dissemination of disease. None of these had received an aromatic diamidine. Nine had fair to poor results (recurrent or active disease present following surgery, requiring further therapy), and one had a serious post-operative complication (broncho-pleural fistula and empyema). The remaining 25 (54 per cent of the resected group) have apparently achieved arrest of their disease for periods of time ranging from a few months to four years or more following treatment.

Case reports from the literature concerning 70 patients with cutaneous or systemic blastomycosis who were treated with stilbamidine, in addition to five of our own, and 31 treated with 2 hydroxystilbamidine plus seven of our own, were analyzed for dosage of drugs given, length of follow-up,

results, and toxic manifestations of the drugs used. Eight apparently had both drugs. Good results, or apparent arrest of disease, were reported in approximately 70 per cent of patients given either stilbamidine or 2-hydroxystilbamidine; poor results (reactivations or continued positive mycologic findings) were noted in 24 per cent of patients receiving the former drug, and in 27 per cent of those receiving the latter. Six of 75 (8 per cent) who had received stilbamidine treatment died, while one of 38 (3 per cent) succumbed after receiving 2-hydroxystilbamidine. Admittedly, the diamidines were administered, in some cases, very late in the course of the disease or in inadequate dosage. The total

TABLE I
PULMONARY RESECTION FOR NORTH AMERICAN BLASTOMYCOSIS

Case No. & Pt.'s Initials	Age, Race, Sex	Chest X-ray	Laboratory**			Drug Therapy***	Operation	Course & Complications	Follow-up	Results
			Sputum	Skin Test	Serology					
1. HJE	39 WM	Cavity RUL	+	+	—	HSB	Segmental Resection & wedge RUL	BPF with empyema; post-resection thoracoplasty done	6 mos.	Good
2. VR	42 NM	Atelectasis RUL	+	—	+*	KI	Right Pneumonectomy	Dissemination of Blastomycosis following surgery	6 mos.	Died
3. JM	33 WM	Cavity RUL	+	—	—	UA	Right Upper Lobectomy	Uneventful Recov. one unconfirmed sputum pos. for B. Dermatitidis	3 yrs.	Good
4. AOP	41 WM	Mass, Left Mid-lung	—	+*	—	UA	Right Pneumonectomy	Dissemination of Blasto. following surgery; cleared with undec. acid	4 yrs.	Good
5. FMP	24 WM	Abscess Cavity RUL	+	—	—	UA SB HSB EV ATB	Right Upper Lobectomy	Sputum positive in spite of all drugs. Clinically well	5 yrs.	Fair
6. OC	38 WM	Bilat. Cavities	+	+	+	KI SB HSB	Right Upper Lobectomy	Sputum pos. post-op. Also pos. for AFB. Clinically only fair.	3 yrs.	Fair
7. PC	60 WM	Right Hilar Mass; Lt. Apical Infiltr.	+	0	0	UA	Right Pneumonectomy	Pt. had pul. tbc. as well as Ca. of lung. Died Pul. Insufficiency 1 wk. post-op.	1 wk.	Died

Notes: Cases 2 and 4 reported in detail previously by Hopkins & Murphy, 1952.

*Post-operatively only
**For Blastomycosis
***Abbreviations:
SB Stilbamidine
HSB 2-Hydroxystilbamidine
UA Undecylenic Acid
KI Potassium Iodide
EV Ethyl Vanillate
ATB Amphotericin-B
BPF Broncho-pleural fistula
+ Positive
— Negative
0 Not done

dosages of drugs used varied from 1.7 Gm. to 22.5 Gm. No obvious correlation was found between total dosage and ultimate results, since in general greater amounts of drug and longer courses were given to patients whose disease reactivated or who did not respond to the initial course of treatment.

Only 40 of the 113 who received aromatic diamidines were followed for longer than one year, and of these, 13 (33 per cent) apparently had one or more recurrences or reactivations following treatment.

Fifty-six per cent of patients who were given stilbamidine were reported to have trigeminal neuropathy—some for as long as four years following its use. Some of them were not protected from sunlight during and following therapy with this drug, a precaution which is said to minimize the incidence and degree of this annoying but not disabling complication. There were only mild toxic symptoms reported following the use of 2-hydroxystilbamidine.

We have not attempted to separate the cutaneous from the systemic or pulmonary forms of blastomycosis because we feel, along with others,[2, 54] that the portal of entry in all cases is probably the lung, except perhaps for inoculation blastomycosis obtained from handling infected autopsy material.

The clinical course of pulmonary blastomycosis is markedly variable. It ranges from the pneumonic form, which occasionally regresses spontaneously and is apparently more responsive to drug treatment, through destructive pulmonary lesions (granulomatous and cavitary) to fatal generalized dissemination. Since there is so much variation in the natural course of the disease, it is not easy to evaluate the efficacy of treatment methods. Nevertheless, the following comments seem to be justified.

1. The present-day treatment of North American blastomycosis still leaves much to be desired. (See Table II).
2. Without much doubt the aromatic diamidines are useful drugs, and produce remissions of blastomycosis fairly consistently in a high proportion of cases. It is a fact, however, that a distressingly high proportion of patients who have been followed long enough, eventually suffer a relapse or a reactivation of disease.
3. Surgery, without drug coverage, can be dangerous because an appreciable number of patients exhibit dissemination of disease following surgery.

TABLE II
RESULTS OF TREATMENT OF NORTH AMERICAN BLASTOMYCOSIS*

Type of Treatment Given	Total Number of Cases	RESULTS (Per Cent of Total Cases)		
		Good or Arrested	Reactivated	Died
Pulmonary Resection**	47	54	22	24
Stilbamidine***	75	68	24	8
Hydroxystilbamidine	38	70	27	3

*Includes Personal Series as well as Collected Cases.
**In 13 patients, an aromatic diamidine was used in addition to surgery.
***In 8 patients, both stilbamidine and hydroxystilbamidine were used.

Our present plan of management for patients who present themselves with pulmonary blastomycosis, is to treat them with one or two courses of 8.0 Gm. each of the less toxic and probably equally effective 2-hydroxystilbamidine, and to remove any resectable cavitary residual, preferably under drug coverage, whether or not blastomyces dermatitidis can be demonstrated in the sputum following drug treatment. A localized noncavitary resectable focus in the presence of positive sputum after at least one course of 2-hydroxystilbamidine is also an indication for surgery. A strong effort is made in lesions of undetermined etiology, to diagnose any possible mycotic infection prior to surgery in order to coordinate diamidine therapy with surgery. A high index of suspicion for pulmonary mycotic disease is helpful in this connection. Drug therapy is administered post-operatively to patients in whom the diagnosis is made only after surgery. A more effective drug than the aromatic diamidines is urgently needed for the treatment of this disease. We are hopeful that amphotericin-B may answer this need, but at this writing we have insufficient data for adequate appraisal of its effectiveness.

II. Coccidioidomycosis

An earlier report on excisional surgery for coccidioidomycosis from this institution was published in 1949.[55] During the past 12 years, 20 cases of pulmonary coccidioidomycosis proved either by mycologic or histopathologic techniques, were seen at Oteen. Eleven of these were subjected to excisional surgery, three for asymptomatic cavities, one for asymptomatic undiagnosed nodules and seven because of recurrent or severe hemoptysis. The courses of five were complicated after surgery—in three, by the occurrence of broncho-pleural fistulas, all requiring thoracoplasty following the resection; in one, by recurrence of cavitation on the side of surgery; and in one, by a residual space, requiring thoracoplasty. There was no death, but of our 11 operated cases, three still require treatment. Two still have broncho-pleural fistulas, with tuberculosis in one, and coccidioidomycosis in the other. The third complains of recurrent hemoptysis from a cavity which developed postoperatively in an adjoining lobe, with sputum positive for coccidioides immitis. This fungus was cultured at some time following surgery from four of our 11 patients. A summary of these results may be found in Table III.

In contrast, of the nine patients on whom only minor, or no surgical procedures were carried out, six are well and sputum negative up to seven years or more following diagnosis; one recently diagnosed case is under treatment for cavitary coccidioidomycosis with amphotericin-B; and two died. One of these died elsewhere of "lung abscess, empyema, and broncho-pleural fistula," but there was no autopsy. This patient had refused surgery for coccidioidal empyema while at Oteen 10 months prior to his death. The other died from pulmonary hemorrhage, and at postmortem, extensive tuberculous as well as coccidioidal lesions were found.

We surveyed the available literature to try to ascertain the experience of others. Approximately 300 cases of pulmonary resections for coccidioidomycosis were collected.[56-81]

The largest group observed by a single team of workers is the series of

TABLE III—PULMONARY RESECTION FOR COCCIDIOIDOMYCOSIS AT OTEEN, NORTH CAROLINA

Case Number & Initials	Age Race Sex	Sputum Exam. for C. immitis	Skin Test (coccidioidin)	Serology**	Chest X-ray Film and Indication for Surgery	Operation	Course and Complications	Follow-up	Results
1. HW	25 NM	+	—	—	Cavity RLL; asymptomatic	Right Lower Lobectomy	Sputum remained positive 3 mos. or more, post-op.	5 yrs.	Good
2. AWB	24 WM	—	—	—	Nodules, RLL of undet. etiology	Excision Nodules RLL	Uneventful	1½ yrs.	Good
3. HLD	24 NM	—	+	+	Cavity RUL of undet. etiol.	Right Upper Lobectomy	Incomplete expansion of lung; thoracoplasty	1½ yrs.	Good
4. DLH	23 WM	+	+	+	Cavity LUL; recurrent hemoptyses	Left Upper Lobectomy	Uneventful	9 mos.	Good
5. HH	22 WM	+	+	—	Cavity RUL	Right Upper Lobectomy	Occasional hemoptyses up to 10 mos. post-op.	10 mos.	Fair
6. JLK	25 NM	+	+	+	Cavity RUL; repeated hemoptyses	Right Upper Lobectomy	Uneventful	2 mos.	Good

7. FEM	39 WM	+	—	—	Cavity Rt; repeated hemoptyses	Rt. Upper Lobectomy; Wedges RML, RLL	Persistent Cavity Rt., continues to have hemoptyses & pos. sputum	18 mos.	Poor
8. BS	35 WM	+	—	0	Cavity LUL repeated hemoptyses	Left Upper Lobectomy	New cavity LLL one yr. post-op.; biopsy pos. for cocci.; sputum pos. AFB for subsequent 9 yrs. persistent BPF	10 yrs.	Poor
9. CY	38 WM	+	+	0	Cavity RUL recurrent hemoptyses	Right Upper Lobectomy	Post-op. hemorrhage; expl. thoracotomy; cardiac arrest & re-suscitation; BPF; Thoracoplasty; BPF persists, pos. for cocci.	1 yr.	Poor
10. NB	32 WM	+	—	—	Cavities, RLL recurrent hemoptyses	Right Lower Lobectomy	Uneventful	10 mos.	Good
11. DC	31 WM	+*	+	—	Cavity RUL; recurrent hemoptyses; sputum pos. AFB	Right Upper Lobectomy	Developed BPF requiring thoracoplasty	5 yrs.	Good

Notes: Coccidioides immitis seen or cultured from specimen in cases 1, 2, 3, 4, 5, 6, 9.
*3 years prior to resection.
**Complement fixation test for coccidioidomycosis.
BPF: Bronchopleural fistula
+ Positive
— Negative
0 Not done

100 cases reported by Cotton, Paulsen and Birsner,[61] Their indications for resection were: giant, secondarily infected, or check-valve cavities; ruptured cavity with pleural effusion, empyema, or broncho-pleural fistula; coccidioidoma; and continued severe hemorrhage from the lung. The number of cases in each group was not given. There was one death in the entire group, and two complications, both involving further cavitation—which was tuberculous in one, and coccidioidal in the other.

Although some of the other reports were also incomplete, approximately 63 per cent of the remaining 216 cases gleaned from the literature were operated upon for cavitary lesions; about 30 per cent for solid lesions; and about 7 per cent for empyema or hydro-pneumothorax. Of this large group, there were serious complications (broncho-pleural fistula, empyema, reactivation or dissemination of disease) in 13 per cent and death occurred in four cases. This appreciable complication rate coupled with the four deaths, gives a five times higher rate of poor to equivocal results than the rate reported by Cotton. The latter feels that this discrepancy can perhaps be attributed to surgical technique, or evaluation of cases. However, since the technique of over 30 different surgeons is involved, we are loath to explain it on this basis, suspecting instead that it reflects accurately the hazard of surgical treatment.

Our attitude regarding surgical intervention for cavitary pulmonary coccidioidomycosis at present, in view of our own experience, and that of the majority of other workers, tends to be conservative. We do not feel justified in recommending resection without definite and rather urgent indications, more especially since dissemination, the one really grave form of coccidioidomycosis, is almost never seen from a chronic pulmonary coccidioidal cavity, and also since the proportion of cavitary cases exhibiting severe symptoms is fairly low. Recurrent hemoptysis, the presence of secondarily infected cavities, or cavity rupture and subsequent empyema or hydro-pneumothorax are definite indications for surgery in our opinion. We do not regard the extremely remote possibility of dissemination, nor minor episodes of streaking as sufficient indications in themselves. Certainly the results of surgery for coccidioidomycotic cavities are much better than those for either North American blastomycosis, or as will be seen subsequently, for pulmonary histoplasmosis. Nevertheless, the appreciable complication and recurrence rate following surgery for coccidioidomycosis, together with the generally excellent prognosis without surgery, makes us feel that surgery should be withheld unless clearly indicated. Undiagnosed solitary or multiple localized nodules should be resected, of course—largely, however, for diagnostic reasons. If their development from a coccidioidal cavity has been observed, they need not be resected.[82] No specific drug has as yet been found to be effective in the treatment of coccidioidomycosis, but preliminary trials with amphotericin-B appear to be encouraging.

III. Histoplasmosis

During the past 10 years a diagnosis of histoplasmosis, based on the identification of Histoplasma capsulatum by histologic, or cultural techniques, was made in 14 patients at Oteen, of whom two died. In 21 others, presumptive diagnoses of histoplasmosis were made, based on clinical,

epidemiological and serological evidence, and of these, none died. Pulmonary resections were done on 16, in 10 of whom the etiologic organism was identified by either histologic or cultural methods. Solitary granulomas were resected in six, and cavitary disease in four. In addition, thoracoplasty was performed for cavitary histoplasmosis with positive sputum in one. Since the clinical picture, the therapeutic implications and possibly, the prognosis of the discrete pulmonary granuloma due to healed pulmonary histoplasmosis (often a "coin lesion" of undetermined etiology until after removal and examination) differs from the chronic progressive cavitary type of disease, we shall consider the two separately. An earlier report from this institution on this type of granuloma was published in 1955.[83]

Our experience with the nodular type of disease parallels that of Forsee and Puckett[84-86] in that in no patient was Histoplasma capsulatum cultured preoperatively and the organism cultured only rarely after surgery, the diagnosis being made on identification of organisms resembling Histoplasma capsulatum in the pathologic specimen. The course of these patients following surgery has been benign in our cases, and apparently in others' series. In one of our cases, in whom the findings of nodular histoplasmosis was incidental to resection for bronchiectasis, a broncho-pleural fistula developed. Pyogenic infection and not mycotic infection was found in the resultant empyema. This required drainage operations and Schede thoracoplasty ultimately. This was the sole complication in this group.

The chronic cavitary form of histoplasmosis is being recognized with increasing frequency, and it constitutes an important problem in diagnosis and management.[87-94] In brief, resections were carried out in four of our patients, and thoracoplasty in one. All had culturally proved histoplasmosis prior to surgery except one, in whom the resected specimen showed cavitary histoplasmosis as well as cavitary pulmonary tuberculosis. One with marked bilateral emphysema, and a huge cavity in the left upper lobe, died on the third post-operative day with broncho-pleural fistula and pulmonary insufficiency. In another, a broncho-pleural fistula also developed which was controlled by thoracoplasty. The patient in whom left pneumonectomy was done for combined histoplasmosis and tuberculosis, had post-resection thoracoplasty to obliterate the pleural space. All three who survived resection have remained well, for from one and one-half to four years after surgery, and the one on whom thoracoplasty was done as the definitive procedure, has had sputum negative for Histoplasma capsulatum, but remains an invalid due partially to the effects of serious pre-existing war wounds.

Reports of pulmonary resections elsewhere in 30 patients and of one exploratory thoracotomy for this type of histoplasmosis were found.[8, 87, 95-104] In two-thirds of these, cultural proof of histoplasmosis was obtained either from sputum or resected specimen, or both and in the remainder, the organism was identified only histologically. There were five deaths in this group; recurrences, reactivations of disease, or progressive disease were seen in five others; and the complication of post-operative empyema requiring thoracoplasty occurred in one case. Bacteriologically proved pulmonary tuberculosis was diagnosed at some time

in the course of the disease in five patients, one of whom succumbed apparently to progressive tuberculosis following operation.

These results, together with those of our series, have been summarized in Table IV. There was no clear-cut evidence of dissemination of disease following surgery in any of the six deaths reported. In this respect histoplasmosis clearly differs from blastomycosis. Nearly two-thirds of the patients were well or improved following surgery, but in one-third, reactivations, recurrences, complications, progressive disease or death followed surgery. Two showed little or no change.

In order to evaluate properly the efficacy of surgical excision in chronic cavitary histoplasmosis, it would first be necessary to have reliable information about the natural course of the disease. In an early study of 11 cases, Sutliff and his co-workers[102] concluded that the course of this form of histoplasmosis was benign and not altered by medical therapy. Nevertheless, in a later study,[7] they reported four deaths in 23 cases studied. These were due to pulmonary fibrosis and emphysema with cor pulmonale in two, with the additional findings of chronic pulmonary arterial thrombosis and abscess due to Micrococcus pyogenes in one of them. A third patient died of causes other than histoplasmosis who also had pulmonary tuberculosis. The cause of death in the fourth was not given. Lehan, Brasher, Larsh, and Furculow reported on a study of 43 cases in the same year,[88] and felt that progression of disease, as evidenced by roentgenographic changes had occurrred in one-fourth, with four deaths in the series. Further details were not given. To date not enough patients have been reported upon to determine accurately the course of cavitary pulmonary histoplasmosis, although Furculow[87] estimates that there are probably approximately 1,200 unrecognized cases in sanatoria throughout the country at present. From the information available, however, it would seem that the overall mortality rate for both surgically and medically treated groups of cases is of approximately the same order (about 10 to 20 per cent) and that most of the deaths are not due primarily to histoplasmosis.

With clearly localized destructive pulmonary lesions, we feel justified in recommending excisional surgery. In this disease, as in the other two, there is an urgent need for a consistently effective drug. If such becomes available it may obviate the need for surgery.

TABLE IV—SUMMARY OF RESULTS OF SURGERY FOR CHRONIC CAVITARY HISTOPLASMOSIS*

Results	Number of Cases	Per Cent of Total
Good or Improved	23	62
Progressive or Unimproved	6	16
No Change	2	6
Died	6	16
Total Number of Cases	37	100

*32 cases collected from the literature, and 5 of our own cases.

SUMMARY

From our experience with 75 patients with pulmonary mycotic infections at Oteen, and from case reports of nearly 500 others in the literature, we have drawn the following conclusions:

1. North American blastomycosis is currently best treated by 2-hydroxystilbamidine, in spite of a relapse rate of approximately 25 per cent. Excision of cavities should be undertaken only after adequate chemotherapy. The surgical mortality rate without drug coverage is 24 per cent, half of it due to dissemination of disease.

2. Excision of coccidioidomycotic cavities should be done if they are very large, secondarily infected, productive of repeated hemorrhages, or have ruptured into the pleural space. Asymptomatic or mildly symptomatic small cavities should probably be left alone. These rarely cause significant symptoms, whereas excision is followed by an appreciable morbidity (13 per cent) and mortality (2 per cent).

3. The need for excision of chronic cavities of histoplasmosis has not been clearly determined. In the absence of specific drug therapy it seems rational to recommend excision of localized destructive lesions.* The mortality rate following excision is 16 per cent.

4. Focal granulomas due to coccidioidomycosis or histoplasmosis need not be resected therapeutically. Since they usually cannot be differentiated from other "coin lesions," resection for diagnosis will often continue to be necessary. This can be done with relative safety.

*Addendum: Since this paper was submitted for publication, a report has appeared which indicates that amphotericin-B may be effective in the treatment of histoplasmosis, as well as in other deep mycotic infections. (Lehan, P. H., Yates, J. L., Brasher, C. A., Larsh, H. W. and Furculow, M. L. Experiences with the Therapy of Sixty Cases of Deep Mycotic Infections. *Dis. Chest*, 32:597, Dec. 1957.)

(We wish to acknowledge the excellent technical assistance of our myocologist, Mr. Carl J. Hogue.)

RESUMEN

Según nustra experiencia con 75 enfermos de infecciones micóticas pulmonares en Oteen, y según lo relatado en 500 casos de otros en la literatura llegamos a las siguientes conclusiones:

2. La blastomicosis es actualmente mejor tratada con 2-hidroxistilbamidina, a pesar de que hay un porcentaje de 25 de recaídas.

La excisión de cavidades debe intentarse sólo después de la adecuada quimioterapia. La mortalidad quirúrgica sin protección por las drogas es de 24 por ciento, siendo la mitad de ella debida a diseminación de la enfermedad.

2. La excisión de las cavidades de coccidioidomicosis debe hacerse si ellas son muy grandes, infectadas secundariamente, sangrantes en volúmenes grandes y repetidos, o han roto la pleura.

Las cavidades asintomáticas o moderamente asintomáticas y pequeñas probablemente no deben tocarse. Rara vez produce síntomas de significación en tanto que la excisión es seguida de morbilidad apreciable (13 por ciento) y mortalidad de 2 por ciento.

3. La necesidad de resecar las cavidades crónica de histoplasmosis no se ha aclarado. En ausencia de tratamiento específico parece racional recomendar la excisión de lesiones destructivas localizadas. La mortalidad después de la excisión es 16 por ciento.

4. Los granulomas focales debidos a coccidioidomicosis o histoplasmosis no necesitan resecarse. Puesto que generalmente no pueden diferenciarse de otras lesiones en "forma de moneda," la resección seguirá siendo necesaria a menudo. Esto puede hacerse con relativa facilidad.

RESUME

L'auteur a tiré les conclusions suivantes de son expérience concernant 75 malades atteints d'infections pulmonaires mycosiques à Oteen, et d'après environ 500 autres observations publiées dans la littérature:

1. La blastomycose Nord-Américaine répond habituellement très bien au traitement par le 2-Hydroxystilbamidine, malgré un taux de rechute d'environ 25%. L'exérèse des cavités ne devrait être entreprise qu'après la chimiothérapie convenable. Le taux de mortalité chirurgicale quand on n'utilise pas les médications est de 24%, dont la moitié est due à la dissémination de la maladie.

2. L'exérèse des cavités coccidioidomycosiques est indiquée quand elles sont très volumineuses, secondairement infectées, causes d'hémorragies répétées, ou quand elles se sont rompues dans l'espace pleural. Les petites cavités asymptomatiques ou s'accompagnant de peu de manifestations devraient probablement être négligées. Celles-ci causent rarement des symptômes importants, alors que l'exérèse est suivie d'une morbidité (13%) et d'une mortalité (2%) appréciables.

3. La nécessité de l'exérèse des cavités chroniques dues à l'histoplasmose n'a pas

été clairement déterminée. En l'absence de traitement médicamenteux spécifique, il semble logique de conseiller l'exérèse des lésions destructives localisées. Le taux de mortalité suivant l'exérèse est de 16%.

4. Les granulomes en foyer dus à la coccidioidomycose ou à l'histoplasmose ne sont pas seulement des indications de résection dans un but thérapeutique. Comme ils ne peuvent pas être habituellement différenciés des autres lésions arrondies, la résection dans un but de diagnostic sera souvent nécessaire. Elle peut être faite avec une relative sécurité.

ZUSAMMENFASSUNG

Auf Grund unserer Erfahrung an 75 Kranken mit pulmonalen Pilzinfektionen in Oteen und an Hand von Krankengeschichten von etwa 500 anderen Fällen der Literatur sind wir zu folgenden Feststellungen gelangt:

1. Die nordamerikanische Blastomykose wird gegenwärtig am besten behandelt mit 2-Hydroxystilbamidin trotz einer Räckfallshäufigkeit von annähernd 25%. Excision von Cavernen sollte nur erfolgen nach entsprechender Chemotherapie. Die Mortalitätsziffer bei chirurgischem Vorgehen ohne medikamentösen Schutz beträgt 24%, von denen die Hälfte erfolgte infolge Aussaat der Krankheit.

2. Eine Excision von kokzidioidomykotischen Cavernen sollte vorgenommen werden, sofert sie sehr gross sind, sekundär infiziert, zu wiederholten Blutungen Anlass gebend und bei Ruptur in die Pleurahöhle. Asymptomatische oder nur mit leichten Symptomen verbundene kleine Cavernen sollte man wahrscheinlich sich selbst überlassen; denn diese verursachen selten stärkere Symptome, wohingegen eine Excision eine beträchtliche Morbiditä (13%) und Mortalität (2%) nach sich zieht.

3. Die Notwendigkeit zur Excision von chronischen Cavernen bei Histoplasmose wurde nicht klar bestimmt. Bei Fehlen einer spezifischen medikamentösen Therapie scheint es rationell, die Excision von umschriebenen destruktiven Herden zu emphehlen. Die Mortalitätsziffer nach Excision beträgt 16%.

4. Fokale Granulome zufolge von Kokzidioidomykose oder Histoplasmose erfordern eine Resektion aus therapeutischer Indikation. Nachdem sie jedoch gewöhnlich nicht differenziert werden können von anderen "Rundherden," wird weiterhin eine Resektion aus diagnostischen Gründen oft notwendig bleiben. Dies kann mit relativer Sicherheit erfolgen.

References will appear in author's reprints.

The Effect of Drugs upon the Infectiousness of Postthoracotomy Pleural Air Spaces and Tuberculous Empyemas

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Since the advent of antituberculosis drugs, postthoracotomy tuberculous empyema has become a relatively rare occurrence. Moreover, the treatment of established tuberculous empyema has been successful. However, although drugs have undoubtedly contributed greatly to the good results, their importance in comparison with surgical factors has not been clearly defined. Hirdes and Bosch[1] concluded that the existence of a postresection pleural space carries little risk of empyema, provided effective drug therapy is administered. Wareham and associates[2] also shared this opinion. Bell and Medlar[3] concluded that postresection space infection almost always occurs in the presence of drug resistant bacilli.

Our experience indicates that early postresection tuberculous complications have not occurred in patients with sputum and resected specimen cultures negative for tubercle bacilli (noninfectious cases).[4] Late bacterial relapses in this group have been exceedingly rare. However, tuberculous empyemas have occurred following resection performed upon patients with sputum or resected lung tissue containing culturable tubercle bacilli (infectious cases).

Materials and Methods

In order to study the effect of drugs in preventing the occurrence of empyema after thoracotomy the postoperative roentgenograms following pulmonary resections and decortications performed upon infectious cases since January 1950 were reviewed. All postthoracotomy air-containing pleural spaces were noted together with their duration. Advent and duration of space infection was determined whenever possible by the results of cultures of the pleural cavity. In many instances when bronchopleural fistula was present it was necessary to base conclusions upon the results of sputum examinations. Under these circumstances infectious sputum was considered evidence of empyema if it became noninfectious concurrently with successful treatment of the space infection. To provide information regarding established infection tuberculous empyemas treated with drugs during the same period were reviewed. Criteria similar to the foregoing were used to determine the existence and duration of pleural infection. Thus it was possible to collect 40 postthoracotomy pleural air spaces which were treated with 43 drug regimens and 16 pleural empyemas treated with 23 drug regimens. The study was limited to the period of the duration of intrapleural air or empyema space.

Bacterial susceptibility studies were performed according to the method previously reported.[5] Resistant tubercle bacilli are defined as those growing consistently in the presence of 10 micrograms of streptomy-

From the Ray Brook State Tuberculosis Hospital.

cin, 10 micrograms of para-aminosalicylic acid and 5 micrograms of isoniazid. Organisms are considered susceptible to pyrazinamide, viomycin, cycloserine, tibione or terramycin if the patient had not previously received those drugs. Effective drugs are defined as those to which organisms are susceptible. Drugs to which organisms were resistant were eliminated from the tables.

Since the extent of pulmonary disease has been shown to influence the results of surgical resection,[5] the amount of disease remaining after thoracotomy was carefully noted with 1 plus representing each estimated quarter of lung volume involved by disease. In the empyemas, a similar method was employed to estimate the volume of the pleural space, including ipsilateral pulmonary disease. Thus in every instance it was possible to estimate the volume of disease within the hemithorax to be studied.

Results

While this series is numerically too small to draw conclusions on a purely statistical basis, the results seem to support certain clinical impressions. Table I summarizes the fates of the 40 postthoracotomy pleural air spaces treated prophylactically by 43 drug regimens for varying periods. Without effective drug therapy all of the spaces became infected, one becoming clinically apparent one year postoperatively. The incidence of space infection was higher with one drug (27 per cent) than with two or more drugs (15 per cent), if one eliminates the two late infections which occurred after short term streptomycin and para-aminosalicylic acid were

TABLE I—POSTTHORACOTOMY PLEURAL AIR SPACES, INCIDENCE OF INFECTION BY DRUG REGIMEN AND TIME OF OCCURRENCE

Effective Drugs at Operation	Total Drug Regimens	Pleural Spaces: Duration (Months Postoperative)									Infections: Time of Appearance (Months Postoperative)									
		0-1	2	3	4	5	6	9	10	12	Total	0-1	2	3	4	5	6	9	10	12
SM	5	1	1	2	1															
PAS	5	3		2							1	1								
INH	3		1		1		1				1				1*					
PZA	9	3	1	1	2	1		1			4	3			1					
SM & PAS	9	2	3	1	1				1	1	4	1		1**					1***	1****
PZA & VIO	3		1		2															
PZA & CYCLO	1		1																	
PZA & PAS	1					1														
SM, PAS, INH	1						1													
No drugs	6	5						1			6	5						1		
TOTAL	43	14	8	6	7	2	2	2	1	1	16	10	0	1	2	0	0	1	1	1

*Organisms became resistant to isoniazid.
**Organisms became resistant to streptomycin and para-aminosalicylic acid.
***Drugs were administered only for the first 3 months.
****Drugs were administered only for the first month.
PZA = pyrazinamide; VIO = viomycin; CYCLO = cycloserine.

discontinued. It is believed this difference could reflect the fact that bacterial resistance tends to occur earlier with single drug than with multiple drug regimens. In support of this contention is the high incidence of infection when pyrazinamide alone was used, since bacterial resistance to this drug occurs early. Also, two patients developed laboratory evidence of drug resistance by the time empyema became clinically apparent. On the other hand, it is evident from the table that empyema can occur under effective drug therapy, a phenomenon which could be related to variations in concentrations of drugs in the tissues and pleural cavity. Although most of the infections occurred within the first month of the existence of a pleural space, the time of their appearance was generally impossible to predict.

Table II summarizes the results of treatment of established tuberculous empyema by various drug regimens. It is interesting that about half of the regimens were successful. Actually, these represent a total of 16 empyemas treated with 23 regimens, of which 11 empyemas were rendered culturally negative for tubercle bacilli. Although some drugs were administered for relatively short periods, and might have yielded better results if continued longer, it appears that combinations which included streptomycin, para-aminosalicylic acid or isoniazid are superior to the others listed.

That the amount of disease remaining in the surgically treated lung influences the incidence of space infection is suggested by Table III. This agrees with our experience with postresection tuberculous complications

TABLE II—TREATMENT OF ESTABLISHED TUBERCULOUS EMPYEMA WITH DRUGS WHILE DEFINITE PLEURAL SPACE EXISTED. EFFECT UPON BACTERIOLOGY

Effective Drugs	Total Drug Regimens	Empyemas: Duration of Treatment (Months)								Cases Rendered Noninfectious: Time after Drugs Started (Months)								
		0-1	2	3	4	5	7	8	10	Total	0-1	2	3	4	5	7	8	10
PAS	1					1												
INH	1		1							1		1						
PZA	2		1	1														
VIO	1						1											
SM & PAS	2		2							2		2						
SM & INH	2			1	1					1			1					
PAS & INH	5	1	2		2					4		2		2				
PZA & VIO	3					1	1*	1		1						1		
CYCLO & TIBIONE	2		1					1										
CYCLO & INH	1	1								1	1							
PZA, VIO, TERRA	1								1**									
SM, PAS, INH	2			1	1					1				1				
TOTAL	23	2	7	3	4	2	2	2	1	11	1	5	1	3	0	1	0	0

*Previously received PZA for 4 months.
**Previously received PZA for 2 months.
Terra = Terramycin.

TABLE III—INCIDENCE OF INFECTION OF PLEURAL AIR SPACES ACCORDING TO THE AMOUNT OF DISEASE IN THE IPSILATERAL LUNG

Amount of Disease	Total Drug Regimens	Total Infections	
		Number	Per Cent
1+	35	12	34
2+	7	3	43
3+	1	1	100
4+	0	0	

in general.[5] Moreover, these results would seem to indicate that these space infections usually originate from the adjacent lung.

On the other hand, Table IV suggests no relationship between size of empyema and results of treatment. This possibly might be due to the fact that empyemas represent tuberculous surface infections which in common with others such as bronchitis, enteritis, and peritonitis respond readily to drug therapy.

Discussion

Experience indicates that postthoracotomy pleural air space is a potential source of tuberculous empyema. In noninfectious cases the occurrence of empyema is exceedingly rare. In the infectious cases antituberculous drug therapy tends to suppress pleural infection for indefinite periods. It may even sterilize the lung and pleura. However, tuberculous empyema does occur in some cases, usually unpredictably. While in many instances empyemas appear concomitantly with the emergence of bacterial resistance to drug being administered, infection may appear while the organisms are drug sensitive. This may be related to the failure of drugs to penetrate into the pleural cavity. Of course, if drug therapy is continued in spite of persistently unresponsive empyema, eventually drug resistant bacilli can be expected to appear in almost every patient.

It seems likely, as in pulmonary tuberculosis, that combinations of drugs yield better results than single effective drugs in the prophylaxis and treatment of tuberculous empyemas. Furthermore, the best results have been obtained when the combinations include streptomycin, para-aminosalicylic acid or isoniazid.

It is interesting to note that while in some instances we have been able to perform without complication pulmonary resections upon infectious

TABLE IV—RESULTS OF DRUG TREATMENT OF PLEURAL EMPYEMA ACCORDING TO THE VOLUME OF THE PLEURAL SPACE AND THE AMOUNT OF DISEASE IN THE IPSILATERAL LUNG

Amount of Disease	Total Drug Regimens	Cases Rendered Noninfectious	
		Number	Per Cent
1+	7	4	57
2+	5	3	60
3+	7	2	29
4+	4	2	50

cases in the absence of effective drug therapy,[5] in this series all of the cases with pleural space who did not receive effective drug therapy developed empyemas. It is also interesting that all of the latter cases except one had little pulmonary disease in the lung operated upon, a condition which is accompanied by a relatively good prognosis in the absence of residual pleural space.[5] As a result of these considerations it appears that the existence of a pleural space is an important predisposing factor in the development of tuberculous empyemas.

Since the incidence of postthoracotomy empyema seems to increase with residual pulmonary disease, it appears that generally infection spreads to the pleura from contiguous pulmonary tissue.

It would seem that although drug therapy offers protection against empyema, and may indeed cure some of them, an important measure in the prophylaxis and treatment of empyemas is early obliteration of the pleural space. This is especially important in infectious cases. It appears of relatively little importance in noninfectious cases. I agree with Herdes and Bosch[1] to the extent that even after pneumonectomy space filling thoracoplasty is rarely necessary in noninfectious cases. However, in the infectious cases I still believe in early obliteration of the pleural space.

The measures which have been found efficacious in preventing the occurrence of postthoracotomy pleural air spaces have been described elsewhere.[4] These consist essentially of extensively freeing the lung when pleural symphysis exists, and carefully controlling air leakage from the pulmonary surface. This allows the remaining lung to expand fully, reaccommodating itself to the pleural cavity. In addition mediastinal shift and diaphragmatic elevation can compensate for a surprising amount of resected pulmonary tissue. Sometimes it is not necessary to free the lung from the diaphragm, as the latter will often rise considerably provided the costophrenic angles have been freed. Often after right upper lobectomy or segmental resection of either upper lobe, merely freeing the oblique fissure and middle lobe or lingula will allow the latter structures to ascend into the apex of the pleural cavity rendering extensive freeing of the lower lobe unnecessary. However, extensive lysis of adhesions is probably the most important method of insuring against postthoracotomy residual air space. If in addition, two tube intrapleural suction is used with negative pressures to 40 centimeters of water as previously described[4] neither "reconstruction"[6] nor "reconstitution"[3] of the lung are necessary. Since collections of blood have potentialities similar to air in the pleural cavity, we have used the Bovie coagulation unit to control chest wall bleeders. Occasionally, when it is not considered desirable to completely free the lung of adhesions we have performed a small thoracoplasty either at the time of resection or shortly thereafter as an alternative method of eliminating dead space.

Although the measures listed by Franz and Murphy,[7] including intrapleural injection of dyes, thoracentesis and bronchography have been found helpful in identifying bronchopleural fistulas, it is believed that the best aids in diagnosis are serial roentgenography and sputum bacteriology. In most instances a pleural space is readily visualized in the early postoperative period, and in patients having no other obvious source of infectious sputum the advent or persistence of infectious sputum almost invariably

heralds the occurrence of a tuberculous empyema and bronchopleural fistula. It is believed that if these methods of diagnosis are adopted the incidence of "occult" or "hidden"[3, 7] bronchopleural fistula should diminish to a very small number.

SUMMARY

1. The natural history of postthoracotomy pleural air spaces and empyemas in infectious cases is reviewed with an attempt to evaluate the effect of drug treatment. The effect of drugs, although generally beneficial, is unpredictable.
2. Obliteration of the pleural space is an important part of the prophylaxis and treatment of empyema. Methods are discussed.
3. Infections of postthoracotomy pleural spaces appear to originate from contiguous lung tissue.
4. Early diagnosis of postthoracotomy empyema can be accomplished best by serial roentgenography and from sputum bacteriology.

RESUMEN

1. Se hace una revisión a través del tiempo de los espacios pleurales con aire y los empiemas para valorizar el efecto del tratamiento con drogas. El efecto de las drogas aunque generalmente benéfico es impredecible.
2. La obliteración del espacio pleural es muy importante para el tratamiento y la profilaxis del empiema. Se discuten los métodos.
3. Las infecciones del espacio pleural después de la toracotomía parecen originarse en el tejido pulmonar vecino.
4. El diagnóstico temprano del empiema después de toracotomía puede hacerse por las radiografías en serie y por la bacteriología del esputo.

RESUME

1. L'auteur reprend l'étude de la plèvre après thoracotomie et épanchements purulents dans les maladies infectieuses, en tentant d'évaluer la valeur du traitement médical. L'effet des médications, bien que généralement favorable, est imprévisible.
2. L'oblitération de l'espace pleural est une part importante de la prophylaxie et du traitement de l'empyème. Les méthodes en sont discutées.
3. L'infection des espaces pleuraux après thoracotomie semble provenir du tissu pulmonaire voisin.
4. Le diagnostic précoce de l'empyème après thoracotomie peut se faire de la meilleure façon par la radiographie et l'étude bactériologique de l'expectoration.

ZUSAMMENFASSUNG

1. Übersicht des natürlichen Verlaufes von pleuralen Luftansammlungen und Empyemen in infizierten Fällen nach Thorakotomie mit einem Versuch, die Wirkung der medikamentösen Therapie zu ermitteln. Wirkung von Medikamenten, auch wenn sie im allgemeinen günstig ist, lässt sich nicht vorausbestimmen.
2. Obliteration des Pleuraspaltes ist ein entscheidender Teil der Prophylaxe und Behandlung des Empyems. Diskussion über die Methoden.
3. Infektionen von Pleuraspalten nach Thorakotomie dürften ihren Ursprung nehmen von ansteckungsfähigem Lungengewebe.
4. Frühzeitige Erkennung von Empyemen nach Thorakotomie lässt sich am besten erreichen durch Röntgenbildreihen und bakteriologische Sputumuntersuchung.

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Treatment of Clotted Hemothorax with Fibrinolysin

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The lysis and aspiration of a clotted hemothorax by means of an effective enzymatic agent is highly desirable. Various enzymes have been used for this purpose but all have certain disadvantages. Trypsin has an irritative effect of pleural pain on injection and often shows a toxic reaction due to the enzyme or breakdown of protein products.[1] The inhibitor (antitrypsin) normally present in the serum or exudates rapidly increases in concentration after the use of trypsin.[2] This may require an increasing dosage of trypsin with successive treatments.

Streptokinase-streptodornase acts primarily as an activator and depends on plasminogen in the wound exudates.[3] Occasional pyrogenic reactions are encountered with this enzyme.[4] Inhibitors to streptokinase are also present in many patients who have had streptococcal infections.[5]

The proenzyme, profibrinolysin, circulates in human and animal plasma. Proenzyme becomes activated during life or after death of the organism. Some of the known activators are streptokinase, staphylokinase, cytofibrinolysokinase, epinehprine, chloroform and potassium cyanide.

Dastre[6] noted the proteolytic substance of blood serum and named this fibrinolysin. Loomis isolated the active proteinase in 1946.[7]

Fibrinolysin is an euglobin, soluble in saline and when mixed with antibiotics loses little activity. Fibrinolysin attacks only fibrin, fibrinogen or prothrombin.[8]

The following animal experiments were done to simulate postoperative and traumatic clotted hemothorax and to assess the effectiveness of fibrinolysin solution.

Experimental Method

A standard hemothorax was produced in the following manner.[9] Blood was drawn into sterile beakers from donor dogs, covered and allowed to clot. These clots were refrigerated for 24 hours. Well formed serum free clots weighing from 96 to 300 grams were obtained. These clots were then placed by a left thoracotomy into the pleural cavity of 16 dogs. At the time of death or sacrifice both chest cavities were explored for residual fluid or clot. Previous experimental studies show that air or fluid may often readily pass to the opposite side of a dog's pleural space.[10] Preliminary *in vitro* studies were done to determine the proteolytic effect of bovine fibrinolysin solution on clotted dog's blood. Clots weighing 200 grams were incubated at 37°C. without agitation in 200 units of fibrinolysin solution and were reduced approximately by one-fourth in 24 hours. Control clots of the same weight under similar conditions but without fibrinolysin failed to show any liquefaction.

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Series I—Table I

Eleven dogs had left thoractomy and left lower lobectomy. A preformed serum-free clot was placed in the pleural cavities of all these animals in order to simulate a postoperative clotted hemothorax. No attempt was made to pleuralize the bronchial stump after lobectomy. Daily intramuscular injections of 600,000 units of procaine penicillin were given up to one week. On the first postoperative day multiple site aspirations were done to determine if any spontaneous liquefaction had occurred. Fibrinolysin, 200 units diluted with saline to a volume of 20 cc., was then injected into the left lower chest, except in dog No. 69 where 400 units of fibrinolysin was used. Daily multiple site needle aspirations were then done until the animal died or was sacrificed.

One dog died seven days postoperatively from atelectasis and pneumonia. The remainder of the animals were serially sacrificed. In all animals the original clot was effectively reduced by the lytic action of fibrinolysin solution. None of the animals showed any impairment in wound healing. All of the unpleuralized bronchial stumps showed varying stages of healing. All the animals showed expanded functioning lungs with little pleural reaction except dogs No. 131 and No. 136 (atelectasis or pneumonia).

Series II—Table II

Five dogs had left thoracotomy performed with placement of a preformed serum free clot in order to simulate a standard traumatic hemothorax. Multiple serial aspirations were done on the first postoperative day up to the time of sacrifice. Fibrinolysin solution 200 units diluted to a volume of 10 cc. was injected into the left pleural space after the first thoracentesis. Fibrinolysin solution effectively lysed the clotted hemothorax in all these dogs. None of the animals in Series I or II showed any objective reactions or pleural pain to the injection of fibrinolysin.

Table I
THORACOTOMY, LOBECTOMY, & INSTILLED CLOT TREATED WITH FIBRINOLYSIN

Dog No.	Wgt. of Clot in Gms.	Total Dosage of Fibrinolysin		No. of Daily Injections	Total Aspirated Vol. in cc.	Fate	Post-Mortem Findings
		Units	Vol. in cc.			Post-operatively	
130	175	200	20	1	10	Killed 3 Days	30gm. clot, 75cc. fluid
131	200	200	20	1	50	Killed 3 Days	5gm. clot, 150cc. fluid
73	96	200	20	1	282	Killed 5 Days	10cc. fluid-atelectasis left upper lobe
48	186.5	200	20	1	71	Killed 5 Days	No clot or fluid
47	109.5	200	20	1	50	Killed 5 Days	50 gm. clot
136	105	200	20	1	50	Died 7 Days	10 cc. clot-atelectasis & pneumonia
98	170	200	20	1	68	Killed 8 Days	23gm. clot, 10cc. fluid
99	158	200	20	1	104	Killed 8 Days	No clot, 75cc. fluid
69	150	400	40	1	42	Killed 12 Days	No clot or fluid
1	150	200	20	1	60	Killed 12 Days	No clot or fluid
126	120	200	20	1	68	Killed 28 Days	No clot or fluid

The assay of antifibrinolysin levels in the blood of the pretreated animals was attempted but discontinued because of technical difficulties. The original thought being a more accurate estimation in determining the dosage of fibrinolysin needed to lyse the hemothorax.

Clinical Experience

Experience in World War II indicated that from 15 to 20 per cent of hemothoraces clot.[11] Organizing hemothorax occurs less frequently in civilian practice. Four clinical cases of clotted hemothorax were treated with fibrinolysin solution.

Case Reports

Case 1: A 34 year old white man was seen four days after injury with right hemopneumothorax. The upper six anterior ribs were fractured. Preliminary multiple level taps failed to aspirate blood. One hundred units of fibrinolysin was injected into the right pleural space the first and second days. Daily aspirations yielded 300, 250, 700, and 280 cc. of blood fluid. A total of 1530 cc. of lysed blood was aspirated with reexpansion of the lung.

Case 2: A 36 year old white man was seen five days after a penetrating wound of the right chest, with hemopneumothorax. Fibrinolysin solution 100 and 200 units was given on the first and third days. Daily aspirations yielded 150, 75, 150, 50 and 200 cc. lysed blood, a total of 525 cc. On the third day he had chills, fever 102°F. and pleural pain after fibrinolysis was injected. The pain lasted several hours and was relieved with intramuscular morphine sulphate grains 1/6. Decortication was done two weeks after admission. An organizing pleural peel and multiloculated cavities were present explaining in part the ineffectiveness of the fibrinolysin solution in dealing with the hemothorax.

Case 3: A 20 year old white man was seen 12 days after upper right anterior rib fracture with hemothorax. One injection of fibrinolysin 200 units was given on the first day. Daily aspirations yielded 850, 30, and 30 cc. A total of 910 cc. of bloody fluid was aspirated and the lung expanded.

Case 4: A 60 year old white man was seen two days after a penetrating wound with left hemopneumothorax. Fibrinolysin solution, 100 units was given on the first and third days. Daily aspirations obtained 200, 150, 750 and 300 cc. of bloody fluid. A total of 1,400 cc. of lysed blood was removed with expansion of the lung.

Fibrinolysin solution in three human hemothoraces proved to be an effective method of removing clotted hemothorax. Failure in Case 2 can probably be explained by the multiloculated cavities making the enzymatic action of fibrinolysin ineffectual. The fever and pleural pain after the intrapleural injection of fibrinolysin solution probably represents an antigenic reaction. Margulis et al[12] have also reported on the effectiveness of fibrinolysin in the treatment of clotted hemothorax.

Table II

THORACOTOMY & INSTILLED CLOT TREATED WITH FIBRINOLYSIN

Dog No.	Wgt. of Clot in Gms.	Total Dose of Fibrinolysin		No. of Daily Injections	Total Aspirated Vol. in cc.	Fate Post-Operatively	Findings
		Units	Vol. in cc.				
50	200	200	10	1	None	Killed 1 Day	No clot or fluid
123	300	200	10	1	None	Killed 3 Days	No clot or fluid
74	150	200	10	1	None	Killed 7 Days	10cc. clot, 8cc. fluid
55	100	200	10	1	None	Killed 15 Days	No clot or fluid
70	250	200	10	1	None	Killed 30 Days	No clot or fluid

SUMMARY

Intrapleural administration of fibrinolysin solution proved to be an effective agent in the treatment of experimental clotted pneumothorax. Clinical application similarly was effective in three of four patients.

RESUMEN

La administración intrapleural de fibrolisina en solución ha mostrado ser un agente efectivo para tratar el neumotórax con coagulos hecho experimentalmente. La aplicación clínica similarmente se mostró efectiva en tres enfermos.

RESUME

L'administration intrapleurale d'une solution de fibrinolysine s'est montrée être un agent efficace dans le traitement du pneumothorax expérimental. L'application clinique fut êgalement efficace chez trios malades sur quatre.

ZUSAMMENFASSUNG

Die intrapleurale Anwendung einer fibrinolytischen Lösung erwies sich als ein wirksames Mittel bei der Behandlung eines experimentell verklebten Pneumothorax. Die klinische Anwendung war ähnlich wirksam bei drei von vier Kranken.

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Comparative Study of Concentrations in the Blood of Para-Aminosalicylic Acid in Tuberculous Patients

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In the Hospital Obrero of Lima we studied patients to determine concentration of PAS in blood plasma with the administration of its different forms. Sodium PAS was administered to nine patients, pure buffered PAS to 12, and PAS-K to six.

The pure PAS used was buffered parasal with aluminum glycinate and calcium carbonate (Parlam-Panray); Sodium PAS was the usual and PAS-K was also of Parlam Laboratories.

Every chemotherapeutic preparation was suspended four days before the test, after which 4 grams of para-aminosalicylic acid were administered every eight hours, by supplying eight capsules of pure buffered PAS, and 11 capsules of 0.50 or 5.5 grams of sodium PAS, each eight hours, and for two consecutive times. Four, six and eight hours after administration of the last dose, 6 cc. of blood were extracted. With PAS-K 11 capsules were administered every eight hours, following the same procedure as sodium salt, but the drug was suspended 48 hours before.

The technique used was the same as that of Deeb and Vitagliano.[1]

The following were the results:

WITH PURE BUFFERED PAS 4 GRAMS EACH 8 HOURS			WITH SODIUM PAS 5.5 GRAMS EACH 4 HOURS		
at 4 hrs.	6 hrs.	8 hrs.	at 4 hrs.	6 hrs.	8 hrs.
5.40	3.70	2.20	4.98	1.12	0.75
5.64	1.30	0.70	3.00	1.50	1.00
10.25	7.33	7.14	1.59	1.41	1.22
6.39	4.70	3.76	2.63	0.94	0.65
6.48	3.95	2.23	3.76	1.12	0.56
5.92	2.35	1.78	3.00	0.94	0.66
7.14	4.70	2.28	5.07	2.63	1.22
3.57	1.90	0.75	3.94	0.94	0.54
10.00	3.00	1.80	2.22	1.41	0.84
3.76	1.69	0.90			
4.23	1.50	1.03	——	——	——
68.78	36.12	24.61	29.13	12.11	7.74
		Averages			
6.25	3.26	2.23	3.23	1.34	0.86

WITH POTASSIC PAS-K 5.5 GRAMS EACH 8 HOURS

At 4 hrs.	6 hrs.	8 hrs.
3.76	2.63	2.16
4.23	1.31	1.02
9.02	2.35	1.03
4.04	2.53	1.50
3.48	1.88	0.90
3.76	1.88	0.60
28.29	13.58	7.21
	Averages	
4.71	2.08	1.20

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SUMMARY

1. Sodium salt as well as potassium PAS, in doses of 5.5 grams every eight hours as also pure PAS in doses of 4 grams every eight hours, provide therapeutic levels in plasma for four hours.

2. Therapeutic concentrations in plasma have been maintained for six hours, with 5.5 grams of PAS-K and 4 grams of pure buffered PAS every eight hours.

3. Concentration in plasma surpassed its therapeutic level for eight hours only with administration of pure buffered PAS 4 grams every eight hours.

4. Therapeutic concentrations in blood maintained during the 24 hours could make possible a more effective action of PAS, protecting the associated drugs employed, SM or INH against the resistance of tubercle baciili.

RESUMEN

1. El PAS sódico, y el potásico a la dosis de 5.5. gramos cada ocho horas así como el PAS ácido puro a la dosis de 4 gramos cada ocho horas, proporcionan niveles terapéuticos en el plasma por cuatro horas.

2. Se han mantenido concentraciones terapéuticas en el plasma por seis horas con 5.5. de PAS-K y con 5 gramos de PAS puro con substancias buffer cada ocho horas.

3. La concentración en el plasma sobrepasó le nivel terapéutico por ocho horas sólo con la administración de PAS puro "buferizado" a razón de 4 gramos cada ocho horas.

4. Las concentraciones terapéuticas en la sangre, mantenidas durante 24 horas podrían hacer posible un efecto mejor del PAS, protegiendo las drogas asociadas, Estreptomicina o Isoniacida contra la aparición de resistencia del bacilo.

RESUME

1. Le P.A.S. sodique aussi bien que le P.A.S. de potassium aux doses de 5,5 grammes toutes les huit heures, ainsi que le P.A.S. pur, aux doses de 4 grammes toutes les huit heures, apportent des concentrations thérapeutiquement valables dans le plasma pendant quatre heures.

2. Des concentrations thérapeutiques dans le plasma ont été maintenues pendant six heures avec 5,5 grammes de P.A.S. au potassium, et 5 grammes de P.A.S. pur toutes les huit heures quand il s'agissait de P.A.S. stabilisé.

3. La concentration plasmatique dépassait son niveau thérapeutique pendant huit heures avec l'administration seule de P.A.S. pur stabilisé à la dose de 4 grammes toutes les huit heures.

4. Des concentrations thérapeutiques maintenues dans le sang pendant les 24 heures pourraient rendre possible une action plus efficace du P.A.S. en empêchant les médications associées streptomycine ou isoniazide, de provoquer la résistance des bacilles tuberculeux.

ZUSAMMENFASSUNG

1. Natricum-Salz ebenso wie Kalium-PAS in Mengen von 5,5 g alle acht Stunden und ebenso reine PAS in Mengen von 4 g alle acht Stunden gewährleisten therpeutische Blutspiegelwerte für 4 Stunden.

2. Therapeutische Plasmakonzentrationen blieben sechs Stunden bestehen mit 5,5 g PAS-K und 5 g reiner gepufferter PAS alle acht Stunden.

3. Plasmakonzentration übertraf ihr therapeutische Höhe in acht Stunden nur bei Anwendung reiner gepufferter PAS 4 g alle acht Stunden.

4. Therapeutische Blutkonzentrationen, die für 24 Stunden anhielten, könnten einen stärker wirksamen PAS-Einfluss möglich machen. Sie würden die mit ihr zusammen gegebenen Arzeneimittel, SM oder INH, gegen eine Resistenz der Tuberkelbeziellen schützen.

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Postinflammatory Tumor (Xanthoma) of Lung

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The wide utilization of lung biopsy for solitary pulmonary nodules not only necessitates familiarity with the more frequent entities producing such a configuration but also those which are less commonplace. An unusual example of the latter is the so-called postinflammatory tumor or xanthoma of lung. Reference to these lesions as tumors is done in the generic sense since it is most likely that they do not represent true neoplasms but a response to inflammation. Macroscopically, they appear as well circumscribed, nonencapsulated, solitary, homogeneous, yellow-tan or white nodules, which may be as large as 7.0 cm. in diameter, within the pulmonary parenchyma. Their histologic appearance is characterized by varying numbers of lipid-laden histiocytes, other inflammatory cells and collagenization. There is no specific symptom attributable to these lesions and they may be only fortuitously discovered in roentgenograms performed for other reasons, or as in the case to be presented, during the course of an exploratory thoracotomy. Not infrequently an antecedent history of pneumonia or other respiratory infection is noted.

Only seven examples of such a pulmonary lesion have been previously recorded, and these are epitomized in Table I.[1-6] Recently, Liebow and Hubbell[7] have described the clinical and pathologic features of seven examples of a somewhat similar pulmonary tumor which, because of a predominant vascular structure, they have designated as sclerosing hemangiomas of lung. These have not been tabulated since it is not unlikely that they represent a distinct entity. Similarly, the pleural nodules described by Brown and Johnson[8] have not been included because of their location, although the cogent possibility exists that they may represent pleural counterparts of these pulmonary lesions.

It appears worthwhile to call attention to this type of pulmonary nodule by recording another example. Awareness of such a lesion should minimize the possibilities of its misinterpretation as a malignant neoplasm, particularly in rapid frozen sections performed at the time of thoracotomy. Certain features of this case allow for comments relative to its etiology.

Case Report

A 59 year old negro was admitted to the hospital complaining of cough productive of moderate amounts of greyish-white sputum and pain in the lower right chest of two weeks duration. There had been no hemoptysis, chills or fever. He had been treated eight years previously with malaria for syphilis of the central nervous system. An x-ray film of the chest performed at that time was not remarkable.

Physical examination revealed dullness to percussion and coarse rales over the right lower lung field. Systolic murmurs were audible over the apex and aortic area. His temperature was 101°F., pulse 88 per minute and blood pressure 150/60 mm. Hg.

Laboratory examination disclosed a red blood cell count of four million with 11 grams of hemoglobin. Leukocyte count was 7,600 with a normal differential. Blood

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cholesterol was 200 mg. per cent with 160 mg. per cent of esters. Urinalyses and serologic tests for syphilis were negative. Sputum examination by direct smear and culture was negative for acid fast bacilli, although pneumococci and beta hemolytic streptococci were identified. Cytologic examination of sputum for tumor cells on four successive occasions was negative. A blood culture revealed pneumococci sensitive to penicillin in vitro.

X-ray film of the chest on admission revealed a uniform opacity obliterating the right lower lung field.

He was treated with penicillin and streptomycin which resulted in subsidence of symptoms in three days. Nevertheless, repeat roentgenograms of the chest revealed interlobar fluid on the right with incomplete resolution of the pneumonic process. Continuation of antibiotic therapy subsequently resulted in clearing of the pneumonic process one month later. However, pleural thickening persisted (Fig. 1). He was bronchoscoped, but no abnormality was encountered. A lung biopsy one week later, revealed a firm nodule measuring approximately 2.0 cm. in diameter within the pulmonary parenchyma of the right lower lobe beneath the diaphragmatic pleura which was excised. Frozen section diagnosis at the time of operation was "xanthoma" of lung. The thoracotomy wound was closed and the patient discharged one week following operation in good health without respiratory complaints. A follow-up examination months later was negative. An x-ray film of the chest at that time revealed slight thickening of the right costophrenic angle as noted previously.

Microscopic Examination: The specimen consisted of a moderately firm nodule measuring 1.75 cm. in diameter. Its outer surface was covered in part by a portion of compressed lung measuring 1.0 cm. in thickness. Its cut surface was smooth, homogeneous, flat and yellow-tan.

Microscopic Examination: Sections stained with hematoxylin and eosin revealed aggregates of moderately large histiocytes with centrally placed, round nuclei and abundant foamy cytoplasm (Fig. 2). This latter appeared red in frozen sections of formalin fixed tissue stained by the oil red O technic for lipids (Fig. 3). Negative results were obtained with the Schultz modification of the Liebermann-Burchard reaction for cholesterol and/or esters and in paraffin sections stained with oil red O and Sudan Black B. Endothelial-lined spaces of simple structure were sparsely scattered throughout. Perls reaction for iron was negative. A moderate number of fibrocytes, plasma cells and lymphocytes and irregular strands of collagen were also observed

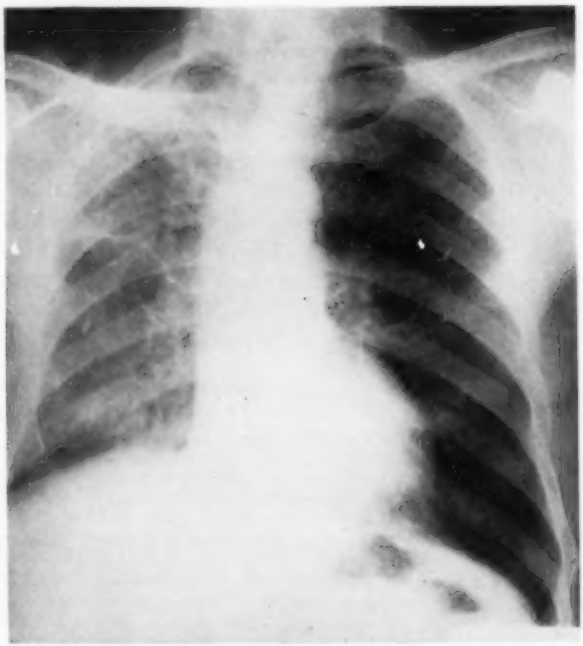

FIGURE 1: Roentgenogram one month following pneumonia revealing pleural thickening. No tumor is evident.

TABLE I
POSTINFLAMMATORY TUMORS (XANTHOMA) OF LUNG

Author	Age	Sex	Symptoms	Site	Size (cm)	Microscopic Features	Term	Etiology	Treatment
Brunn, H.[1]* (1939)	5	F	Cough, fever	RUL	5	Fibroblasts; inflam. cells; hemorrhage	Benign neoplasm†	Neoplasm?	Lobectomy, no recurrence 2 yrs.
Csermely, H.[2] (1941)	37	M	"Fibroma" removed 7 yrs. ago	RUL	Lobe?	gran. tissue; fibroblasts; lymph.; plasma cells; foam cells	xanthofibroma pulmonis†	xanthomatous degen. of fibroma	Autopsy, death due to meningitis
Scott, Payne & Morrow[3] (1948)	34	F	Pleurisy 11 yrs. ago	RLL	4.5	foam cells; fibroblasts; c. tissue	solitary xanthoma†	primary xanth. deposit or degen. of neoplasm	Lobectomy, no recurrence 9 mos.
Ford, Thompson & Blades[4]** (1950)			Discovered routine X-ray 6 yrs. ago	LUL (lingula)	2.5	foam; cells; fibroblasts; plasma cells	xanthoma†	No comment	Lingulectomy, uneventful
Childress & Adie (1950)	21	M	Cough 8 mos.	RML	4	plasma cells; foam cells; c. tissue	plasma cell tumor†	neoplasm?	segmental resection, uneventful
Umiker & Iverson[5] (1954) Case 1:	24	M	Cough 2 mos.	RUL	3	fibroblasts; foam cells; plasma cells; hemorrhage	post-inflammatory tumor	inflammation	Lobectomy
Case 4:	41	M	Pneumonia 22 yrs. ago; bronch. adenoma 2 yrs. ago	RLL	7	fibrolasts; foam cells; c. tissue; hemorrhage	post-inflammatory tumor	inflammation	Lobectomy no recurrence 1 yr.
Fisher & Beyer (1957)	59	M	Lobar. pneumon. 1 mo. ago	RLL	1.75	foam cells; c. tissue plasma cells; lymphs	post-inflammatory tumor	inflammation	Excision; no recurrence ½ yr.

*Case 2 of Umiker & Iverson.
**Case 3 of Umiker & Iverson.
†Considered as postinflammatory tumors by Umiker & Iverson.

coursing throughout the aggregates of foam cells. The lesion was not encapsulated but surrounded by compressed pulmonary parenchyma. The latter revealed many anthracotic-laden histiocytes and a moderate number of lymphocytes and plasma cells within alveoli. Sections stained by the Wilder reticulum method revealed an irregular, haphazard distribution of reticulum fibers. Less frequent elastic fibers were observed to be similarly distributed throughout the lesion in sections stained by the Verhoeff-von Gieson method (Fig. 4).

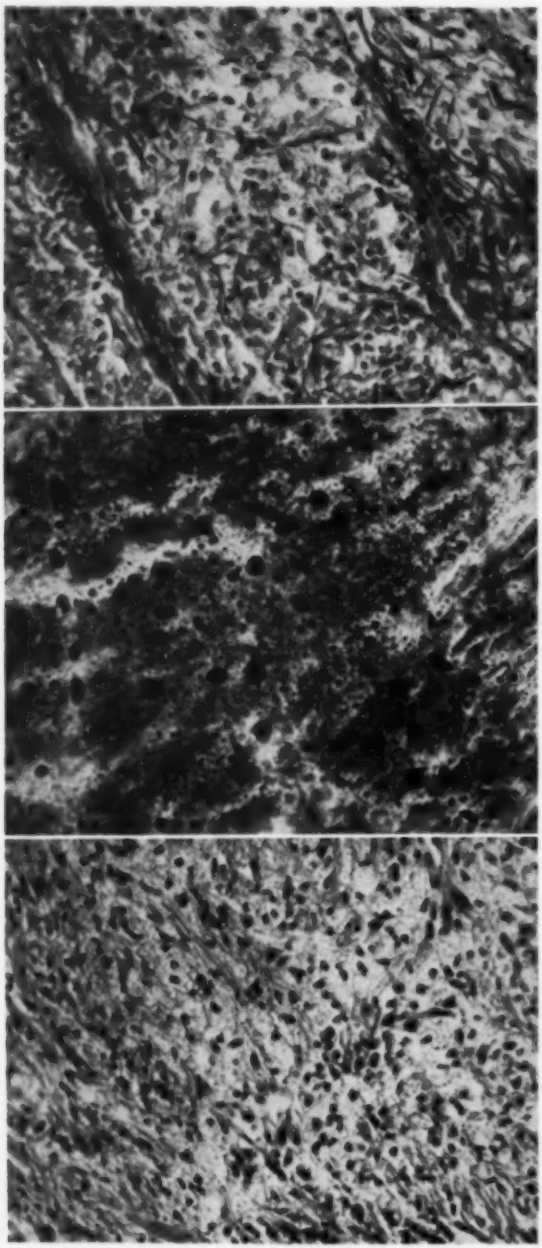

FIGURE 2

FIGURE 3

FIGURE 4

Figure 2: Photomicrograph of postinflammatory tumor revealing principally histiocytic (foam cell) structure. Some plasma cells and strands of collagen are also evident (X220).—*Figure 3:* Section of lesion stained with oil red O revealing intracellular lipid (appearing black) (X220).—*Figure 4:* Section stained by Verhoeff elastic tissue method revealing dispersed fragments of elastic fibers among foam cells (X220).

DISCUSSION

Concepts concerning the etiology of these pulmonary lesions are varied. Umiker and Iverson[6] referred to them as postinflammatory tumors, considering that they represented a response to inflammation. They indicated that their morphologic components were not different from those encountered in other forms of pulmonary inflammation. Liebow and Hubbell[7] however, have raised the possibility that they may be the results of inflammatory changes within pre-existing vascular tumors which they designated as sclerosing hemangiomas. They cited the occurrence of collagenization and foam cell infiltration of vascular tumors of other sites, notably the brain, and the frequent history of pulmonary infection in patients with these lesions as being compatible with such a pathogenesis. Although they made analogies between these pulmonary lesions and the more frequent sclerosing hemangiomas of the skin, it appears germane to note that the examples of the former depicted by them appear more reminiscent of true angiomas than the unique dermal lesion characterized by curlycues of collagen about small and frequently occult vascular channels. Instead, Case 7 of their report had been recorded previously[9] as a capillary hemangioma of the lung. On the other hand, the vascular pattern in the case presented, as well as other examples of postinflammatory tumors, appears to be no more conspicuous or unusual than that which might be expected to be associated with inflammation. Such information suggests that the lesions described by Liebow and Hubbell[7] may represent an entity distinct from the postinflammatory tumors.

There is no evidence to suspect that such lesions may be the result of either a primary or secondary disturbance in lipid metabolism. Hypercholesterolemia was not encountered in this or the other example[3] in which such a blood determination was performed. In addition, other stigmata of such a metabolic disturbance were not evident. The pulmonary alterations recently described by Renzetti, Eastman and Auchincloss[10] in histiocytosis-X (Schüller-Christian Disease) indicate extreme interstitial fibrosis resulting in impairment of alveolar-capillary diffusion, features not apparent in this or other cases of the solitary postinflammatory tumors.

It is also highly untenable that such lesions are the result of a form of lipid degeneration of a pre-existing epithelial neoplasm. Epithelial elements have not been observed in any previously recorded case. Similarly, identifiable areas of such mesenchymal neoplasms as the neurilemoma, in which histiocytic foci are not unusual, have not been noted. The presence of elastic fibers as indicated by Umiker and Iverson[6] might also be considered as evidence against their neoplastic nature. Comment relative to the possibility of such changes occurring within a primary vascular tumor, as suggested by Liebow and Hubbell,[7] has been made above.

Designation of these lesions as postinflammatory tumors as suggested by Umiker and Iverson[6] has merit. It aptly implies their etiology and circumvents usage of such restrictively descriptive terms as histiocytoma or xanthoma since other inflammatory components may predominate. In this regard it is of interest to note that perhaps many of the instances of so-called plasmacytoma of lung represent postinflammatory tumors in which plasma cells constitute an outstanding morphologic feature. One of the cases reported by Childress and Adie (see Table) as plasmacytoma was considered by Umiker and Iverson[6] as representing an inflammatory rather than neoplastic lesion, a view also held by Stewart[11] and emphasized by Spyker and Kay[12] in their recent review of previously recorded cases of pulmonary plasmacytoma. In addition, the term "xanthoma" is conventionally reserved for those lesions of metabolic origin.

The torpidity and self limited nature of the postinflammatory tumors are reflected by the case observed by Ford and associates[4] in which no change in the roentgenographic appearance of the lesion was noted during a period of six years. No examples have demonstrated local invasiveness or metastatic spread. The uneventful course exhibited by the patient in this report following simple excision of this lesion indicates that a minimal operative procedure may be sufficient for its treatment.

The necessity for an awareness of this type of rare pulmonary nodule is obvious if diagnostic and therapeutic errors are to be avoided.

SUMMARY

An example of a solitary postinflammatory tumor of the lung histiologically comprised of lipid-laden macrophages and lesser numbers of other inflammatory cells and collagenization is presented. The clinical as well as histologic features of seven other previously recorded cases are reviewed. It is considered that such lesions represent a response to inflammation rather than true neoplasm, lipid deposit resulting from a metabolic disorder or a "xanthomatous degeneration" of a primary lung tumor. The recognition of this unusual and rare type of pulmonary nodule appears imperative if errors in diagnosis and consequently treatment are to be avoided.

RESUMEN

Se presenta un caso de una tumoración post-inflamatoria del pulmón que histológicamente consistía en macrófagos cargados de lípidos así como células inflamatorias en

menor número y colagenización. Las características clínicas e histológicas de otros siete casos antes referidos, se revisan. Se considera que tales lesiones representan una respuesta inflamatoria más bien que neoplasia verdadera, resultados depósitos de lípidos por un trastorno metabólico o una "degeneración xantomatosa" de un tumor primario del pulmón.

El reconcimiento de esta forma unisitada y rara de nódulo pulmonar, parece imprerativa si los errores de diagnóstico son de evitarse y por consecuencia el tratamiento.

RESUME

Les auteurs présentent un cas de tumeur isolée post-inflammatoire du poumon constituée histologiquement par des macrophages chargés de graisses, avec d'autres cellules inflammatoires en moins grand nombre, et par du collagène. Les symptômes cliniques, aussi bien qu'histologiques de sept autres cas antérieurement rapportés sont rappelés. Les auteurs considèrent que de telles lésions représentent une réponse à une inflammation plutôt qu'un véritable néoplasme, un dépôt lipoïdique résultant d'un désordre métabolique ou de la "dégénérescences xanthémateuse" d'une tumeur pulmonaire primaire. La reconnaissance de ce type inhabituel et rare de nodule pulmonaire semble capital pour éviter les erreurs de diagnostic et par conséquence de traitement.

ZUSAMMENFASSUNG

Vorstellung eines Beispieles eines solitären Lungentumors nach Entzündung, der histologisch lipoid-geladene Macrophagen und eine kleine Zahl von anderen entzündlichen Zellen und Bindegewebsbildung enthielt. Die klinischen sowohl wie die histologischen Merkmale von 7 anderen zuvor mitgeteilten Fällen werden einer Durchsicht unterzogen. Es wird in Betracht gezogen, dass solche Veränderungen eher eine Antwort auf die Entzündung darstellen als wirkliche Neoplasmen; die Lipoidablagerung ist die Folge einer Stoffwechselstörung oder einer "xanthomatösen Degeneration" eines primären Lungentumors. Die Erkennung dieses ungewöhnlichen und seltenen Typs eines pulmonalen Knotens erscheint von Wichtigkeit, wenn Irrtümer in der Diagnose und der daraus folgenden Behandlung vermieden werden sollen.

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Some Thoughts on Results Following Intermittent Streptomycin in Pulmonary Tuberculosis

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The contribution made by streptomycin (SM) towards the success of antituberculous chemotherapy is by now well established. It is not an "all safe, all powerful" drug, as its use can lead to serious consequences. There appears to be some danger from toxicity of the drug itself, but in our experience this has been relatively low. However, the dosage of streptomycin when used intermittently (two or three injections per week) in combination with daily INH and/or PAS is generally inadequate and invites therapeutic failure. This results in the patient's excreting organisms resistant to one or more of the principal antimicrobial agents. Retreatment is rather difficult, the percentage of success being comparatively low; and surgery in these patients carries a definite risk of postoperative complications such as bronchopleural fistula and empyema.

One sees a number of private physicians and chest hospitals throughout the country using combinations of drugs including biweekly streptomycin, believing this to be "adequate" initial treatment in tuberculosis. The reason is difficult to understand. Papers have been published to confirm the earlier findings of the British Medical Research Council—that intermittent SM with daily INH or PAS is *not* the treatment of choice in tuberculosis.[8]

We have reviewed 108 cases who were admitted to National Jewish Hospital consecutively since 1956, whose sputum was initially positive for typical *M. Tuberculosis*, and whose previous chemotherapy had included intermittent SM (1 gm. two or three times per week). Positive culture on admission was found in 79 per cent of these cases, and all but five of these were excreting high proportions of tubercle bacilli resistant to SM and/or INH. In 21 per cent of these cases the treatment had been apparently successful and their sputum tests were consistently negative for tubercle bacilli.

An additional group of 46 cases was studied whose initial chemotherapy including intermittent SM was started after January 1955 (i.e. after the publication of the M.R.C. findings). Sixty three per cent of these patients were found positive for tubercle bacilli on admission, and all but three were resistant to SM and/or INH (Table I). The treatment was started at home for 14 of these patients, and in hospital for 32.

Many factors may explain why certain principles are not more widely accepted in the United States, and among these is the fact that reports observed by us in the American literature do not sufficiently stress the superiority of the regimens containing daily SM over all others. One argu-

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ment presented in favor of other regimens is the idea of holding one's 'major' drug for future needs. Of course this is not necessary if one can achieve a conversion rate of approximately 99 per cent in previously untreated cases by applying appropriate and adequate chemotherapy.[9]

One of the writers has had some experience in chest work in England and Australia, and certain groups there, too, at one time believed biweekly SM with daily INH or PAS to be good treatment. This practice has become much less frequent in the last two years or so, though such a combination is occasionally used at the tail end of the initial treatment with daily SM plus INH and/or PAS. Lately the use of intermittent SM is being abandoned in preference to daily INH plus PAS. One can also mention that in these countries practically every case picked up by private practitioner, mobile survey, etc., is referred to the area chest clinic for investigation and appropriate treatment. Therefore there is a better chance for such treatment to be applied according to uniform standards.

Several reports have been published dealing with studies carried out by the M.R.C. in England,[1-3] to assess the clinical potentialities of SM, INH and PAS. This comprehensive work outlined the results of the principal controlled trials. Some of the most important findings were as follows: (1) At six months, only two of the 12 positive cultures from patients treated with daily SM plus INH contained organisms highly resistant to INH, compared with eight out of nine from those treated with biweekly SM plus daily INH; (2) There was substantial bacteriologic and radiographic evidence.

It was clearly established that biweekly SM with daily INH was much less satisfactory in preventing the emergence of INH resistant organisms. In addition the M.R.C. showed that daily SM with INH was superior to all dual drug combinations at the six month period. Since then other independent groups, including National Jewish Hospital, have confirmed these findings.[7-10]

It is our opinion that intermittent streptomycin should not be used in moderately advanced or far advanced tuberculosis. If it is desirable to avoid daily injections in minimal disease, then one should use daily INH with PAS since this combination has been proved more effective than intermittent SM with INH or PAS. One should not be lulled into believing that high dosage INH might permit the use of intermittent SM. Biehl et al.,[11] has shown that such a combination has an equal number of treatment failures.

The therapeutic drive against tuberculosis cannot approach 100 per cent success if inadequate treatment is given initially. It is generally felt that

TABLE I

YEAR	DISEASE CLASSIFICATION			PREVIOUS THERAPY			SPUTUM CULTURE ON ADMISSION		DRUG RESISTANCE			DRUG SUSCEPTIBILITY
	Far Adv.	Mod. Adv.	Min.	Int. SM	INH	PAS	Pos.	Neg.	SM	INH	PAS	
1955	8	6	—	14	14	9	13	1	11	13	5	—
1956	11	14	—	25	21	14	17	8	13	14	4	2
1957	4	3	—	7	6	4	2	5	1	1	1	1
Totals	46			46			32	14				3

early institutional treatment is to be preferred for the majority of patients suffering from pulmonary tuberculosis.

SUMMARY

1. A review of National Jewish Hospital cases is presented, showing an incidence of drug resistance of over 63 per cent in those cases admitted, whose initial treatment elsewhere had included intermittent streptomycin.
2. The importance of initial "adequate" therapy is emphasized. It is our opinion that intermittent streptomycin should not be included in any initial treatment regimen.

RESUMEN

1. Se presenta una revisión de los casos del Hospital Israelita mostrando una frecuencia de la resistencia a las drogas de más de 60 por ciento en los casos admitidos que habían sido tratados antes en otra parte de manera inicial incluyendo el uso de la estreptomicina intermitente.
2. Se recalca la importancia de hacer un tratamiento inicial "adecuado." En nuestro concepto la estrepotomic ina intermitente no debe ser usada en cualquier régimen de tratamiento inicial.

RESUME

1.—L'auteur passant en revue les cas de l'Hôpital National Juif montre la fréquence bactérienne atteint 63% des malades hospitalisés, dont le traitement initial avait comporté en tout cas de la streptomycine administrée de façon intermittente.
2.—L'auteur souligne l'importance de la thérapeutique convenable appliquée dès le début de la maladie. A son opinion, la streptomycine administrée de façon intermittente ne devrait pas être admise dans le programme thérapeutique du début de l'affection.

ZUSAMMENFASSUNG

1. Es wird eine Übersicht des Nationalen Jüdischen Krankenhauses vorgelegt, die ein Vorkommen von Arzneimittel-Resistenz nachweist bei mehr als 63% solcher Zugänge, bei deren auswärts eingeleitete Behandlung intermittierendes Streptomycin einbegriffen war.
2. Die Bedeutung der einleitenden, adäquaten Therapie wird hervorgehoben. Nach unserer Überzeugung sollte intermittierendes Streptomycin in irgendein einleitendes Behandlungschema nicht einbezogen werden.

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Lung Abscess in the Mentally Ill as a Complication of Electric Shock Treatment*

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Physicians dealing with the mentally ill patient often are painfully aware of how difficult is the early diagnosis of lung abscess. Furthermore, the need for early diagnosis is urgent since delay in treatment may bring about the need for pulmonary resection.

In a review of the literature dealing with lung abscess following electric shock treatment we found only 34 cases. However, a survey of lung abscesses at this hospital during the past two years showed 15 cases occurring following electric shock treatment. This experience leads us to believe that lung abscesses following electric shock treatment are more common than the literature indicates.

A survey was undertaken to determine the factors involved in the production of these lung abscesses. Oral sepsis is a common occurrence in the mentally ill and provides a ready source of bacteria for pulmonary infection should they find access to the lungs. In addition, periods of unconsciousness are more frequently observed in the mentally ill than in the non-mentally ill. Alcoholic intoxication, attempted suicides (barbiturates) and epilepsy produce their share of the unconscious periods observed. The administration of electric shock treatment results in a period of unconsciousness with an almost explosive inspiration which follows a short period of apnea. These factors set the stage for pulmonary aspiration and lung abscess. To further complicate the situation, mentally ill patients, following their initial aspiration, seldom cough; expectorate little and rarely complain.

Sixty per cent of our collected lung abscesses followed electric shock treatment. Since this treatment is under the control of the physician we are thus particularly concerned with the mechanisms involved in the production of such lung abscesses and practical methods of their prevention.

Method

Our study is divided into two phases. The first phase deals with proof of aspiration occurring following the administration of electric shock treatment. In a group of five patients, Dionosil,® 1 to 2 cc. was introduced into the patient's mouth just prior to the administration of electric shock treatment. In a second group of 10 patients 5 cc. of Dionosil was administered. Chest x-ray films were taken as soon as possible following the patient's return to consciousness. Since Dionosil is radiopaque and easily seen on chest x-ray films, this offered an excellent opportunity to verify that pulmonary aspiration of oral contents does occur following electric shock treatment.

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®Aqueous suspension of propyliodone—Glaxo Laboratories, Ltd., Greenford, England.

The second phase of the study is a summary of the clinical cases which we observed and treated.

Discussion

In the first group of patients it was found that when the amount of Dionosil was 1 to 2 cc. no aspiration could be demonstrated. With the use of 5 cc. in the second group aspiration into the trachea or lung fields occurred in 40 per cent of the patients following the administration of electric shock treatment. When the amount of radiopaque material was increased to 10 cc. by Kahn[3] the incidence of aspiration was increased to 100 per cent.

These findings indicate that aspiration does occur following electric shock treatment, and that the amount of material in the mouth just prior to the administration of such treatment determines how frequently aspiration will occur.

Since salivation is commonly observed following electric shock treatment and saliva probably acts as a vehicle to help transport bacteria to the lungs, two remedies can be suggested. The first is to reduce salivation by adequate premedication with atropine. Secondly, to have equipment ready to aspirate the patient's mouth immediately following the convulsive seizure, before the patient takes his first breath and can aspirate the saliva (or gastric contents) into his lungs.

Our case material included eight males and seventeen females, representing a cross section from the four southern hospitals which send pulmonary cases to this hospital. Our youngest patient was 14, our oldest, 51. Approximately 60 per cent of these cases developed lung abscesses following electric shock treatment.

Breakdown of the cases as to predisposing etiology was: electric shock treatment, 15 cases; alcoholics, four; attempted suicide, one; cancer, one; epileptics, two and mental defectives, two.

The indicated initial treatment in patients with lung abscesses is bronchoscopy and antibiotics. We feel that bronchoscopy is of particular importance and should always be done, not only for diagnostic, but also for therapeutic reasons. From the diagnostic standpoint it rules out such problems as foreign body, cancer, and endobronchial disease, and offers the opportunity to obtain uncontaminated cultures. From a therapeutic point of view, bronchoscopy serves to aspirate considerable quantities of purulent material, and thus aids in intra-bronchial drainage of the aspirated material from early lung abscess. All of our bronchoscopies were done under general anesthesia, employing pentothal and judicious amounts of anectine during the introduction of the bronchoscope. This was necessary in all cases because our patients were uncooperative.

The time at which the initial treatment is started, following the occurrence of aspiration, is of extreme importance prognostically. We were able with bronchoscopy and antibiotics to bring about resolution and restoration to normal-appearing x-ray films in 10 out of 12 cases if treatment was started within three months of the occurrence of the original aspiration. However, if the initial treatment was started later than three months following the original aspiration, we were required to do a pulmonary resection in every case. This underscores the urgency of early diagnosis and institution of proper and energetic therapy. Furthermore, the fact that in only one case was it possible to do a segmental resection, emphasizes that the amount of surgery required will be extensive.

While the mortality rate for pulmonary resection in our hands was zero (13 cases), certainly this cannot be expected over a larger series of cases. In our entire series of 25 cases, we had one death due to lung abscess, which occurred following closed empyema drainage. Empyema had resulted from rupture of one of the bilateral lung abscesses into the pleural space. This dreaded complication of lung abscess often results in mortality.

A study was made of the effects of various aerosols as to whether they would reduce the need for pulmonary resection when started early in conjunction with bronchoscopy and antibiotics. In approximately half of our patients we added aerosol trypsin to the above mentioned therapeutic regimes in the hope that it might produce some digestion of aspirated material and encourage intra-bronchial drainage. Our statistics indicated that trypsin was of little if any value when administered by aerosol. In other words, the incidence of resolution without surgery in these cases was not improved by the administration of aerosol trypsin.

The possibility of lung abscess should be suspected in a mentally ill patient who is receiving shock therapy and begins to exhibit a sustained elevation of temperature. Such a patient should be considered to have a lung abscess until proved otherwise. The physician should immediately obtain a chest x-ray film in search for lung abscess. The fact that the patient does not cough or expectorate large quantities of sputum, or exhibit an occasional hemoptysis, does not rule out the diagnosis.

We have encouraged our staff to obtain adequate dental surveys prior to the administration of electric shock treatment, and to eliminate oral and dental sepsis. It appears that withholding food and water four hours prior to electric shock treatment, adequate premedication with atropine, and suction equipment, are also worthwhile prophylactic measures. We have noted during the past eight months that the incidence of pulmonary abscesses occurring within our hospital has decreased under such a regimen.

SUMMARY

1. Any patient who is mentally ill and receiving electric shock treatment and develops a sustained elevation of temperature should have an immediate chest x-ray film and should be considered to have pulmonary abscess until proved otherwise.

2. Patients who are to have electric shock treatment should have a dental survey prior to the administration of such treatment.

3. Care should be taken during electric shock treatment to prevent aspiration of oral or gastric contents into the tracheobronchial tree. The greater the amount of material within the mouth just prior to such treatment the higher the incidence of tracheobronchial aspiration.

4. When a patient is found to have a lung abscess, bronchoscopy, aspiration of sputum, cultures, and the administration of appropriate antibiotics are mandatory.

5. Pulmonary resection was required in every case in which bronchoscopy and antibiotics had been delayed longer than three months following the initial aspiration.

6. We believe careful observance of the procedures outlined will reduce the incidence of pulmonary complications following electric shock treatment and reduce the mortality rate when they do occur.

RESUMEN

1. A todo enfermo que siendo un caso mental se haya sujetado a tratamiento por choque eléctrico y presente una elevación de temperatura sostenida, debe hacerse una radiografía de tórax y ha de considerarse con absceso pulmonar hasta que no se demuestre lo contrario.

2. Los enfermos que se sujeten a choque eléctrico deben hacerse una revisión dental previa.

3. Debe tenerse cuidado durante el choque para evitar aspiración de contenidos gástrico u oral dentro del árbol traqueal. Mientras más contenido en la boca antes del tratamiento, mayor es el peligro de aspiración bronquial.

4. Es indispensable hacer broncoscopia, aspiración de esputos, cultivos y administrar antibióticos cuando se encuentre uno de estos enfermos con absceso.

5. Se ha necesitado hacer resección pulmonar en todos los casos en que la broncoscopia y los antibióticos se han retardado más de tres meses después de la aspiración inicial.

6. Creemos que estas precauciones reducirán la frecuencia de complicaciones pulmonares despúés del shock y disminuirán la mortalidad de éstas si ocurren.

RESUME

1. Tout malade atteint de maladie mentale, soumis au traitement par électro-choc, et quiréagit par une élévation de température prolongée, devrait subir immédiatement une radiographie pulmonaire et devrait être considéré jusqu'à preuve du contraire, comme porteur d'un abcès pulmonaire.

2. Les malades qui doivent être soumis au traitement par électro-choc devraient subir un contrôle dentaire avant l'administration d'un tel traitement.

3. Pendant le traitement par électro-choc on devrait prendre soin d'empêcher l'aspiration du contenu buccal ou gastrique dans l'arbre trachéo-bronchique. Plus est importante la quantité de produits contenus dans la bouche immédiatement avant le traitement, plus est fréquente l'aspiration endo-bronchique.

4. Quand on découvre qu'un malade est porteur d'un abcès pulmonaire, la bronchoscopie, l'aspiration des sécrétions, leurs cultures, et l'administration d'antibiotiques appropriés sont impératives.

5. Une résection pulmonaire s'est montrée nécessaire quand la bronchoscopie et les antibiotiques avaient été différés plus de trois mois après l'aspiration initiale.

6. Les auteurs pensent que l'observation prudente des principes qui viennent d'être précisés réduira la fréquence des complications pulmonaires consécutives au traitement par électro-choc et abaisseront le taux de la mortalité si néanmoins elles surviennent.

ZUSAMMENFASSUNG

1. Jeder Patient, der geisteskrank ist, eine Elektroschock-Behandlung bekommt und anschliessend eine anhaltende Temperatur-Erhöhung aufweist, braucht alsbald eine Thoraxröntgenaufnahme und muss bis zum Beweis des Gegenteils als Träger eines Lungenabszesses angesehen werden.

2. Patienten, die für eine Elektroschock-Behandlung vorgesehen sind, benötigen eine Überprüfung des Gebisses vor Anwendung einer solchen Behandlung.

3. Während der Elektroschock-Behandlung muss Sorge getragen werden dafür, dass eine Aspiration von Mund- oder Magen-Inhalt in den Bronchialbaum verhindert wird. Je umfangreicher die Menge von Material in der Mundhöhle ist unmittelbar vor einer solchen Behandlung, um so häufiger ist das Vorkommen einer Aspiration in der Bronchialbaum.

4. Wenn es sich herausstellt, dass ein Patient einen Lungenabszess hat, so ist die Bronchoskopie, Sputumaspiration, Kulturverfahren und die Verwendung von entsprechenden Antibiotizis dringend.

5. Eine Lungenresektion war in jedem Fall erforderlich, bei dem mit der Bronchoskopie und den Antibioticis länger als drei Monate nach der initialen Aspiration gezögert worden war.

6. Wir sind der Überzeugung, dass eine sorgfältige Beobachtung der mitgeteilten Massnahmen das Auftreten von pulmonalen Komplikationen im Anschluss an Elektroschock-Behandlung und die Mortalitäts-Ziffer verringern wird, sofern es überhaupt dazu kommt.

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Artificial Coughing, A New Apparatus for Paralyzed Patients*

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Patients with respiratory paralysis (for example in poliomyelitis) are unable to cough. Bronchial secretions may accumulate and cause atelectasis, bronchopneumonia, decreased gaseous exchange, blood vessel shunt phenomena, and other undesirable effects. Such complications are responsible for a large percentage of the deaths associated with prolonged artificial respiration. Coughing is the best way to keep the bronchial tree clean and to prevent pulmonary complications. Patients with tracheotomy or endotracheal intubation are unable to cough because they can not close the glottis, and coughing is possible only when contraction of the abdominal wall works against a closed upper airway.

Barach, Beck, Bickerman and co-workers, have recently reported good results with mechanical coughing by means of the "coughing chamber"[1] (essentially a modified iron lung) and of the "Cof-flator,"[6] the first real coughing machine. Another coughing apparatus was developed in 1955 by Stoffregen and Oehmig and reported at the 1955 World Congress of Anesthesia at Scheveningen, Netherlands.[11]

Description of Apparatus:

This apparatus consists of a manually operated valve, which opens suddenly connecting the bronchial tree to a source of negative pressure. This sudden large pressure difference between the inside of the lungs through the upper airways to the coughing apparatus simulates normal coughing. The required pressure difference is achieved by means of a surgical as-

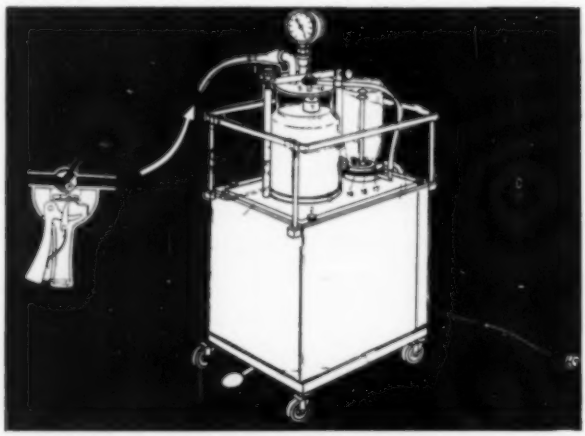

FIGURE 1: The artificial coughing apparatus, consisting of a surgical aspirator and a pistol-like valve.

*Presented at the 23rd Annual Meeting, American College of Chest Physicians, New York City, May 29 to June 2, 1957.

pirator (suction machine) with a vacuum flask of five liters capacity. A relief valve maintains a flask pressure of minus 200 centimeters of water. By means of a new three-way valve and a rubber hose the trachea of the intubated or tracheotomized patient can be exposed suddenly to the vacuum (Fig. 1). This new valve (Fig. 2) is a pistol-like, manually operated instrument, consisting of a trigger mechanism, a blocking lever, and a three-way valve. One arm leads to the room air, to an anesthesia machine, or to a mechanical respirator. When the trigger is pressed, the blocking lever opens the rotary valve in about 0.05 second. The patient's lungs are

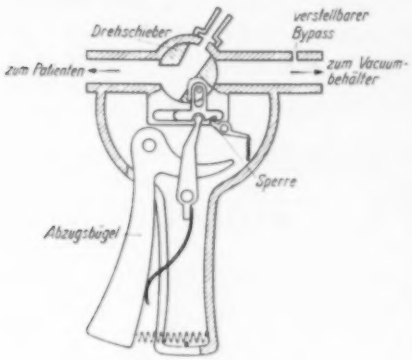

FIGURE 2A

FIGURE 2B

Figure 2: The pistol-like valve.

Translation:

Drehschieber	— rotary valve
zum Patienten	— to the patient
zum Vakuumbehälter	— to the vacuum flask
verstellbarer Bypass	— variabel bypass
Abzugsbügel	— trigger
Sperre	— blocking lever

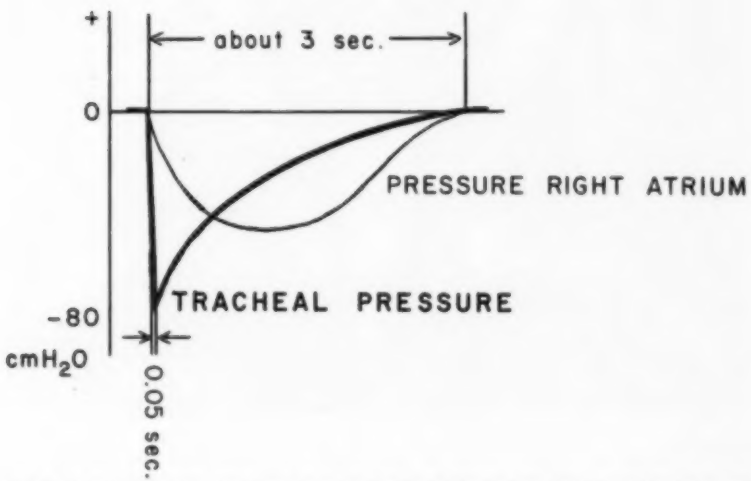

FIGURE 3: Pressures in the trachea and in the right atrium during artificial coughing.

now suddenly connected to the suction apparatus and artificial coughing is produced.

It might appear that a preliminary insufflation of the lungs in order to dilate the bronchial tree would give a more efficient cough. However, experiments proved this to be unnecessary, the coughing by means of negative pressure only is practically as good.

Figure 3 shows the pressure changes in the trachea and in the right atrium, measured by means of a cardiac catheter. The difference in the pressures and in the time is due to various resistances, mainly the elasticity of the lungs and thoracic wall. Figure 4 are pneumotachograms showing that the artificial coughing is practically identical with spontaneous cough.

The danger of pulmonary edema as a result of repeated negative pressure was feared by Scandinavian clinicians who hesitated to apply even much

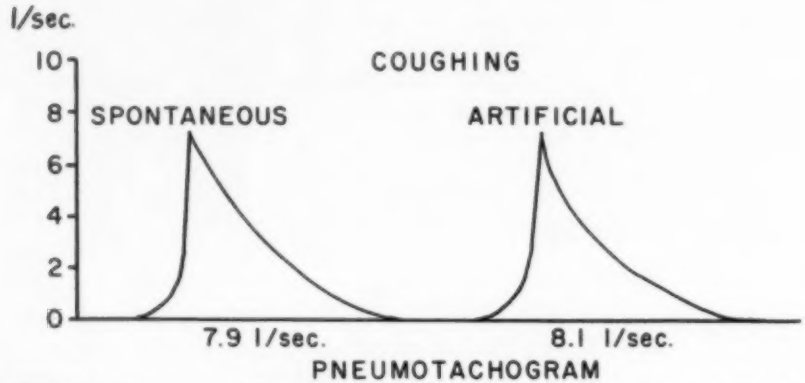

FIGURE 4: The curves for spontaneous and artificial coughing are practically identical.

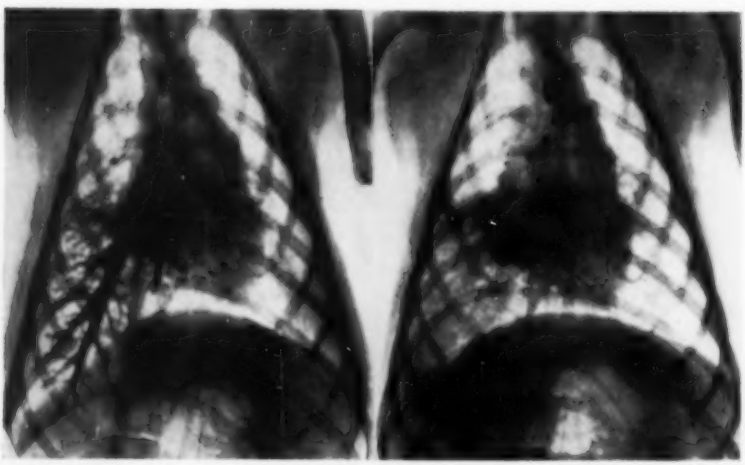

FIGURE 5A, *left:* X-ray of the chest of an anesthetized, intubated, curarized dog. The right middle and lower lobes are filled with a contrast medium.—FIGURE 5B, *right:* The contrast medium has been removed by artificial coughing. The same findings have been demonstrated by cinematographical technique.

less suction than this apparatus uses during artificial breathing. Fortunately, this complication has not appeared. Hoernicke and Stoffregen[14] tested the present instrument on a large number of guinea pigs, and produced brief endotracheal pressures up to 300 cm. H_2O suction. In some cases, this was repeated 20 times in 10 minutes. No change of the lungs are found by histological examination and estimations of the fluid content in the lungs by weighing and dessication. This technique of artificial coughing was also used in a few hundred patients, in poliomyelitis, and in curarized tetanus patients but mainly during or at the end of anesthesia. No sign of pulmonary edema was found in any of these patients.

SUMMARY

A new artificial coughing device is described. It removes secretions from the lungs of intubated or tracheotomized patients. The device consists of a pistol-like valve connected to a vacuum source and is efficient, inexpensive, and easy to operate.*

*This artificial coughing device is now manufactured by the Draegerwerk Luebeck, West Germany, under the name "Tussomat."

Note: Figures 2 and 5 are published with the permission of Springer-Verlag, Heidelberg, Germany.

RESUME

L'auteur décrit un nouvel appareil provoquant la toux artificielle. Il permet ainsi d'évacuer les sécrétions des poumons chez les malades intubés ou trachéotomisés. L'appareil consiste en une valve semblable à un pistolet reliée à une source de vide; c'est un appareil efficace, peu couteux et facile à manier.

ZUSAMMENFASSUNG

Beschreibung einer neuen künstlichen Hustenvorrichtung. Sie entfernt das Sekret aus Lungen von intubierten oder tracheotomierten Kranken. Die Vorrichtung besteht aus einer mit einem Vakuum-Erzeuger verbundenen revolverartigen Klappe und ist von guter Wirksamkeit, preiswert und leicht zu handhaben.

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The Individual Man and Medicine*

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It is incumbent upon me first to express my deep appreciation of the honor of presenting to this distinguished body, the American College of Chest Physicians, the third Louis Mark lecture. It had not been my good fortune to know Dr. Mark, but in reading something of his life and works I have been impressed by his great versatility, his humanity and his understanding and, above all, by an inquiring mind intensely interested in the complexities of human nature which requires a fine appreciation of the individual. For this reason it has seemed appropriate to discuss in a memorial to such a man certain aspects of individuality, not in an environmental, behavioristic or psychological sense, but as to man's physical constitution and variation. In doing so I do not overlook the cognate subject of biochemical individuality, which I touch upon only casually because of the limitations which must necessarily be set in an address such as this. In examining some of the origins and factors concerned in matters of human physical constitution, I shall have occasion to illustrate some of the principles by reference to the genesis of cardio-vascular anomalies in the hope that the subject matter may not seem to be too remote from the field of immediate concern and interest to the chest physician. If I should falter by lack of clarity or over-simplify in order to be clear, I would crave your indulgence.

Not quite 200 years ago, Giovanni Battista Morgagni (1682-1771), the great physician of Forli, entered his 80th year and, as though to celebrate the full ripening of his years and wisdom, published one of the most significant books in medical literature. This book, *De sedibus, et causis morborum per anatomen indagatis* (Venice, 1761), or in English entitled "On the seats and causes of diseases investigated by anatomy," introduced, as Rudolf Virchow (1821-1902) put it, the "anatomical idea" into medical practice, but even more importantly, it so profoundly influenced medicine that we have scarcely recovered from the revolution which his ideas engendered. Although Morgagni, in giving credit to his predecessors Antonio Benivieni (c. 1440-1502), Andreas Vesalius (1514-1564), and Theophilus Bonetus (1620-1689), modestly disclaimed any great originality, he had in fact initiated the destruction of the individual as the object of scientific medical pursuit and investigation. Prior to Morgagni, the physician had thought in the Hippocratic tradition, in terms of the patient as a sick individual; after Morgagni, disease came to be regarded as the effect of a pathological process affecting an organ. Henceforth we would speak of diseases of the stomach, of the liver, of the lungs, and, if we failed to determine the "seat" of the disease, we could always avoid the patient by considering his syndrome. The further transition was gradual, for within a generation Morgagni's concept of the diseased organ had been carried by the Frenchmen Marie-François-Xavier Bichat (1771-1802) and

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Jean Cruveilhier (1791-1873), into the tissues. Thence, the extension of the cellular theory of Matthias Schleiden (1804-1881) and Theodor Schwann (1810-1882) into a cellular pathology at the hands of John Goodsir (1814-1867) and Virchow, passed disease to the cells and, finally, to their ultimate physico-chemical constitution. If during this transition we have lost the individual, we have gained immeasurably in scientific precision to a point where some 20 years ago there was great optimism that man and all his biologically relevant processes could be interpreted by sufficiently accurate physical laws so that medicine and human biology would be fully scientific. But this optimism has been sorely misplaced so that physicians have shifted instinctively back to the concept of the whole man, as did their forefathers, with uncertain leanings on a psychosomatic prop which would not destroy their ideal of a fully scientific and materialist medicine.

Edwin Schrödinger,[1] the distinguished physicist and Nobel laureate, points out that these optimistic expectations that biological processes are interpretable in terms of physical and chemical law would be regarded today not only as naïve, but definitely wrong. These opinions were based upon the *a priori* view that because of the "cosmical" number of atoms involved in biological processes, "all the revelant laws of physics and physical chemistry would be safeguarded even under the very exacting demands of statistical physics in respect of large numbers." However, it has now been demonstrated that incredibly small numbers of atoms may play a dominating rôle in orderly biological processes. Such small numbers control observable developmental features of the organism and important characteristics of its physiological functions. Thus C. D. Darlington[2] estimates that the volume of a gene is approximately that of a cube whose edge is 300 Å. This dimension is roughly only 100 to 150 atomic distances in a liquid or solid so that if a gene were a homogeneous liquid it would contain only a million or so atoms. But the gene is almost certainly a large protein molecule in which every atom and every radicle plays an *individual* rôle. Ignoring the unwarrantable neo-vitalistic implications of Schrödinger's discussion, there is much substance in his remark that the number of atoms is "much too small (from $\sqrt{n}$ point of view) to entail an orderly and lawful behavior according to statistical physics—and that means according to physics." The recent brilliant work of Heinz Fraenkel-Conrat[3] in Berkeley on viruses indicating that the nucleic acid fraction comprising but 4 per cent of the protein molecule is the operative factor, further emphasizes these facts.

The growth of Mendelianism into the modern science of genetics is very recent and has served somewhat to redress the balance in our thinking between the individual and the category by emphasizing inherited traits and characteristics, overt or recessive. In the sphere of teratology and malformation genetic concepts and mutation theory have played a most significant rôle in shaping our understanding, but by the same token, concepts of a predetermined individual and, by transference, interpretations of anomalies such as those which are so frequent in the cardio-vascular system, have brought about a nihilistic attitude as to possibilities of prevention except through mechanical means as exemplified by surgical procedures.

An archaic memory in the collective mind of medicine of the existence of the individual would obtrude itself from time to time. It sought to emphasize the individual by classification of man into several sub-types, each of which possessed a characteristic morphology reflecting an individualized physiology and temperament. This movement was carried to absurdity by Cesare Lombroso (1836-1909) who, in attempting to establish the constitutional basis of criminality, insanity and genius, thought he could determine whether the subject was destined to be hanged by the degree of adherence of the lobule of the ear. Nevertheless, Lombroso's imaginings had their useful effects in the development of techniques for the recognition of the individual by Bertillon (1886) and Francis Galton's method (1892) of identification by fingerprints. Heirs to the conception of constitutional types have long been with us. In our own time, Bryant[4] and Goldthwaite[5] were influential, if not very successful, in individualizing lesions of the back and locomotor system to herbivorous, carnivorous and omnivorous types of mankind as a substitute for the sthenic and asthenic classification of an earlier generation. And now among the latest recruits are W. H. Sheldon (1940, 1954)[6] with his great refinements of somatotype into endomorphic, mesomorphic and ectomorphic varieties in agreement with the germinal layers and thus possessing viscerotonic, somatotonic and cerebrotonic temperaments supposedly either to enjoy, or to act, or to think in consonance with their physical constitution.

Then we have the attempt of Behnke[7] and associates (1942) to establish criteria of individual constitution in terms of the active tissues of the body by calculating "lean body mass," which is body mass minus the fat, as obtained by densiometric methods or derived (Miller and Blyth 1952)[8] from studies of basal oxygen consumption. To these must be added the index of Tanner (1951)[9] in which the degree of masculinity or femininity of the individual is rated by means of a formula reflecting the relationship between shoulder width, pelvic dimensions and leg length, so as to reveal the andric or masculine and the gynic or feminine components admixed in the individual.

It will be observed that in all these attempts to analyze constitution, there is the implication that the morphology of the individual is related to individual physiological function. Sheldon's classification stresses not only the organ derivatives of viscera, muscle and brain from the tripartite germinal layers but inherently the physiological action of these systems, and Tanner evidently is concerned with body form as an expression of endocrine balance. Doubtless the implication has justification on empirical grounds for we are all familiar with the effects of metabolic, endocrine and other factors on body form. Nevertheless, the conception is in many respects too crude in view of the enormous number of variables and one cannot escape the thought that dimension is not necessarily related to function, as evidenced by the well known example that the size of the brain is in no way correlated with the quality of the mind. Although generalizations on individual constitution may have some degree of validity, we must proceed with the very greatest caution since knowing so little of the mechanisms responsible for human variation we may be greatly misled. In order to test some of the assumptions, Milton DeLucchi,[10] working in my department, investigated constitutional variation in rela-

tionship to the circulatory responses caused by orthostatic stress. The circulatory system was selected because it readily manifests by the quantitative changes in pulse rate, pulse pressure and in the ratio of pulse product to mean pressure, the ability of the individual to withstand gravitational forces in adjusting to the erect posture. Failure to adjust rapidly to the experimental conditions brings on the classical "effort syndrome" described by Lewis. In the eighty subjects examined and classified by such constitutional measurements as somatotype, index of lean body mass and index of androgyny, statistical correlations to the physiological response of the cardio-vascular system either did not exist or, where they did exist, could be explained as due to other purely physical factors inherent in the system of constitutional classification such as total height and relative size. Of great importance, and contrary to expectation, no relationship could be established between mesomorphy and lean body mass, and the correlation between cardio-vascular response and both mesomorphy and lean body mass was negative. In view of the fact that mesomorphy and the index of lean body mass are ostensibly a measure of muscularity, the failure to find any correlation with the preeminent mesodermal cardio-vascular system is disturbing. I quote this work not only because of my personal relationship to it but as the most complete investigation carried out in this connection. It should remind us of the great difficulties associated with any analysis of individual constitution.

Although we are unable to relate differences in constitutional morphology to physiological action with any great degree of success, there is very good evidence for a biochemical and metabolic individuality. Ever since the discoveries of Maragliano (1892), Landsteiner (1901) and Eisenberg (1901) on haemolysis and agglutination leading to blood-grouping, blood as such has ceased to exist, to be replaced by blood-type now refined to individual varieties of very great complexity, but it was Sir Archibald Garrod (1902)[11] who, in announcing the existence of inborn errors of metabolism, suggested that "just as no two individuals of a species are absolutely identical in bodily structure, neither are their chemical processes carried out on exactly the same lines," thus restoring concepts of diathesis and idiosyncrasy which a generation earlier Sir Jonathan Hutchinson (1881)[12] in his essay on the "Pedigree of Disease" had sought to destroy. Since the beginning of the century the amount of circumstantial evidence which has accumulated is impressive. It has been shown that the range of values for blood sugar, uric acid, serum amylase, alkaline phosphatase, cholinesterase, β-glucuronidase, among many others, is relatively constant for the individual and these values may be well above or below accepted levels. Variations are often in excess of 30-fold, which would seem to indicate that the failure to individualize many of our common biochemical tests has left us with parameters which are entirely too coarse. Transplantation experiments (Loeb 1945),[13] the response to drugs (Williams 1956),[14] the allergies and numerous other investigations establish the view that every individual possesses his own metabolic pattern. From such considerations Leo Loeb (1945) in discussing the biological basis of individuality emphasizes that organisms which are highest on the evolutionary scale possess the greatest degree of biochemical individuality, and Roger Williams (1958)[15] has recently proposed that the

individual metabolic pattern can lead the way to a chemical, as distinct from a physical, anthropology.

All, I think, will agree that the individual is an aggregation, genetically determined, representing the sum of morphological, physiological and biochemical characteristics. These characteristics in combination are peculiar to the individual. In morphological characteristics variation is very great and perhaps the major error which we make is the attempt to relate too closely this variation with physiological and biochemical characteristics. This error is understandable in view of the psychological difficulty of dissociating the morphological appearance of the individual from his total personality. However, if we enquire into the factors guiding the achievement of body form from genetic determinants we shall gain great insight into the meaning of individual variation and important understanding of congenital defects. These factors are the growth differentials and their interaction, timing and the action of the endocrine system and nutrition.

Some years ago in studying the growth of the fetal skeleton, Inman[16] and I were able to establish the fact that the dimensions and angles of various structures increase throughout the fetal period by constant increments in relationship to sitting height. In other words, the curves fitted to the data follow straight lines and can be represented by the empirical equation of the general form $D = aL + b$ where a is a constant representing the slope of the curve and hence the rate of growth of that part. These rates of change are characteristic for each dimension and their interaction is responsible for the changing bodily proportions of the individual as he passes from fetal to adult life. It is possible to project by extrapolation these rates of change obtained from the fetus forwards into adult life, thus revealing the mechanism whereby the well known differences in facial design and proportions come about. Consequently it is not difficult to appreciate how individual family resemblances as well as body proportions are achieved. These resemblances essentially depend upon the ratio of facial and other dimensions and these ratios, although they are without doubt genetically determined, are achieved by the interaction of the individualized rates of growth of the various dimensions. These rates of growth are, however, only potential and the potentiality may fail to express itself due to nutritional, endocrine, toxic or other disorders. Thus we observe that the human dwarf is round-headed or brachycephalic; the bridge of the nose is flat and the palatal region shortened, causing the upper jaw to be undershot; and the face is characteristically wide and flat, giving the appearance commonly called "dish-faced."[17] In such a description we should recognize that all we are saying is that the fetal features have been retained due to a failure, whether the ultimate cause be endocrine, nutritional, or something else, to achieve the full growth potential of the various skull and facial dimensions.

The specific rate of change affects not only linear dimensions but also processes which interact with dimensional growth. A striking example of this is seen in the relationship of the rate of membranous ossification occurring in the bones of the calvarium in association with dimensional changes. Measurement shows that in the case of all membranous bone of the skull, there is a constant inflection in the growth rate when the individual achieves a sitting height of from 140 to 160 mm. The explanation

of this is seen when the rate of membranous ossification is plotted against the rate of growth of the skull in its circumference. The slowing down of the ossific process is due to the inhibition of the spread of ossification by the formation of the sutures. Obviously, without the inhibition of ossification by the sutures, the bones comprising the vault of the skull would soon fuse into a solid mass of bone permanently limiting further growth of its dimensions, as sometimes is seen in skull anomalies with premature fusion of the sutures. However, it should be observed that the rate of ossification of membranous bone is always greater than the rate of growth in dimension. This is of enormous importance and demonstrates one of the mechanisms of inner consonance which exist in bodily processes; in this instance insuring an adequate bony covering to the calvarium even though there be great variations in the size of the skull. Thus in a microcephalic skull, the membranous bones are soon ossified, having less area to cover, but they do not fuse at the sutures, which permits of some further growth of the skull. While in the case of a hydrocephalic skull of moderate degree the fontanelles are not enlarged nor the sutures widened since the rate of ossification is such that it can cover an area a third greater than that of a normal skull at birth.

The effects of differential rates of growth upon the structure and organization of the individual are profound. It serves to explain such paradoxes of development as why the parathyroid derived from the third or more cephalic of the pharyngeal pouches is inferior or caudal to that derived from the fourth or more caudal pouch. The transposition of the parathyroids is inevitable because the parathyroid III makes its appearance and differentiates earlier than the parathyroid IV in relationship to the growth of the rest of the neck. Minor changes in growth differentials and the timing of the appearance of organ "anlagen" or primordia are undoubtedly responsible for individual differences and variations in bodily structure and, if of slightly greater degree, may produce profound errors of development. This may be illustrated by the congenital anomalies either naturally caused or experimentally induced.

A fantastic and bizarre example of malformation from interference with timing of anlagen is seen in a rare case of penoscrotal transposition where the scrotum has come to lie anterior to the penis. As I showed some years ago (Saunders, et al., 1942)[18] the scrotal elements arise bilaterally, independent of the phallus. Normally the phallus arises first from the genital tubercle and as it enlarges it carries forward a portion of the urogenital sinus to form a part of the future urethra. The scrotal elements appear later and at 15 mm. are seen as bilateral swellings cranial to the phallus. With further growth these swellings, due to differential growth, pass caudally relative to the phallus to occupy the traditional position for the scrotum. Delay in the development of the urogenital sinus leaves the scrotal elements in an anterior position to form a scrotum lying in front of the underdeveloped penis.

Modifications of, or a failure to express, the full potential of growth in proper relationship to other regions may not only affect the bodily proportions primarily concerned but may exercise in a purely secondary manner more distant regions of the body not basically related. This may be illustrated by examination of the genesis of cleft palate. It is usually thought

that cleft palate is due to a primary failure in the development and fusion of the palatal rudiments derived on either side from the maxilla. But this obvious explanation is far from the truth. Cleft palate is the result, not of defective formation of the palatal rudiments, but to a failure of the lower jaw to grow soon enough. This is revealed in studies in our laboratories by Monie and Nelson of anomalies produced experimentally in rat fetuses by transitory deficiencies of folic acid. Normally in both the rat and man, the tongue, which arises from the lower jaw, develops initially within a common naso-buccal cavity. In the interim the palatal rudiments appear and elongate downwards, pressed against the lateral walls, being unable to meet because of the presence of the tongue. The ensuing rapid growth and expansion of the arch of the lower jaw provides accommodation for the further growth of the tongue which now leaves the nasal cavity, releasing the palatal rudiments which, through their innate elasticity and turgor, spring upwards into relationship with one another and eventually, by fusing along their borders, roof the buccal cavity. Failure of the lower jaw to grow rapidly enough leaves the tongue in the nasal cavity, preventing the approximation of the palatal elements. When at length the jaw grows sufficiently to accommodate the tongue, the palatal rudiments on return find that the all-over growth of the rest of the face prevents the rudiments from coming into contact. The palatal elements, no longer subject to the stimulus of growth tension, remain stunted and short, and we have the characteristic and familiar deformity of cleft palate. Minor delays or slight decreases in the rate of growth of the mandible doubtless would lead to the formation of a highly vaulted arch. I am reminded that earlier students of the body constitution regarded a high palatal arch as a serious stigma of mental, moral and physical degeneration, which is illustrative of the weakness of the constitutional bridge over which many have attempted to pass in reaching for understanding of the individual.

Experimental teratogenesis is most revealing of the sort of factors responsible for individual variation and the failure of the individual to reach his full potential of physical development. The grosser degrees of this failure result in congenital anomalies; minor degrees, in the structural variation of the individual. Congenital defects may, of course, cause profound secondary upsets in body physiology which in turn may modify secondarily other parts. However, the distance between congenital defect and individual variation would seem to be only one of degree, and in any one organ the defects and variations, although elaborately and separately classified, are in fact connected to form a continuum of change or spectrum from the normal to variation, to the grossest of abnormal conditions.

The experimental embryologist has long been aware that certain toxic agents, especially those, such as the cyanides, radiation and Trypan blue, which interfere with the oxygen reduction potential of the tissues, will produce a variety of congenital malformations; the incidence of any particular anomaly being related to the period at which the agent is administered. To these we must add the remarkable clinical observations of Gregg in Australia, connecting cataract and congenital heart disease with maternal infection by the virus of rubella. Since then, observers have shown that injury to the fetus may be produced by the withdrawal of a

number of metabolites; vitamin A,[19] pantothenic acid,[20] riboflavin,[21] folic acid,[22] vitamin E,[23] and vitamin B_{12}.[24] It is important to recognize that teratogenic agents are non-specific. Almost all the varieties of malformation observed in man have been reproduced by these experimental means. Further, the maternal metabolic deficiency may be entirely transitory, of but two or three days, with little discernible effect on the mother, yet it will result in severe fetal anomalies which cannot be repaired by the restoration of the metabolite. The critical period for the embryo is short, probably between the second and the eighth week in the human subject, and between the eighth and fifteenth day in rats.

The cardio-vascular anomalies produced in the offspring of rats fed a diet deficient in folic acid (pteroylglutamic acid), studied in our laboratories by Baird et al. (1954)[25] and Monie et al. (1957),[26] even though the deficiency was transient, ran the gamut of virtually all known types of abnormality. Among them have been observed defects of the ventricular and atrial septa, persistence of the truncus arteriosus, double or right-aortic arch, absence of the ductus arteriosus, aberrant subclavian arteries, variations in the arterial arch system, abnormalities of the pulmonary arteries and veins, persistence of the right-umbilical vein, and numerous others. As would be anticipated, deficiencies during the seventh to ninth day while the heart itself is undergoing rapid changes, showed a higher incidence of cardiac defects, whereas deficiencies during the ninth to tenth day were associated chiefly with anomalies of the vascular system.

We should not forget that in the physical development of the individual there is a dynamic relationship forming an endless circle between structure and function. This may again be illustrated by reference to the development of the heart and the genesis of such familiar cardio-vascular anomalies as over-riding of the aorta, transposition of the aorta, persistence of the truncus arteriosus, and the like. In discussing such anomalies, the evolutionist such as Spitzer[27] contends that they constitute a phylogenetic throwback to the heart of reptilia or the fishes, little mindful of the fantastic size of the camel which he asks us to swallow in striving for a gnat of explanation. Spitzer's view is so dominated by the outmoded doctrine of recapitulation that analogies are made which are often unwarrantable. J. E. Frazer[28] pointed this out many years ago in connection with the assumption that the pharyngeal pouches of man were the homologues of the gill clefts of fishes. In the case of the heart, Sir Arthur Keith introduced the conception of the bulbus cordis which, for reasons too lengthy to give here, probably has no equivalent in the human heart. By so doing he introduced much confusion in the understanding of cardiac development and the genesis of these common anomalies.

All who have examined the living fetus are aware that the heart in the earliest stages of formation commences its rythmical contraction to establish a primitive circulation. The first sign of its inner division into a right and left heart is the appearance of the ventral and dorsal endocardial cushions in the walls of the atrioventricular canal. Even prior to their fusion to separate the right from the left atrio-ventricular orifice, the cushions serve functionally to divide the blood stream into two. De Vries and I[29] have studied the fluid dynamics of such streams and have been able to show that, depending upon the angle of approach, the streams

will pass in spiral relationship with one another in a clockwise or counterclockwise direction. The period of the spiral will depend upon the force of the stream. There is little or no admixture of the two streams. Furthermore, in a restudy of the formation of the right ventricle we have been able to show that the development of the right heart is largely dependent upon the rapid elongation of that region hitherto called the bulbus cordis. In the normal heart the approach of the two streams is such as to result in the formation of a moving column of fluid which spirals counterclockwise as it enters the truncus arteriosus. In this way the right or pulmonary stream is directed into the sixth arch and the left or aortic stream into the fourth arch with little admixture of the two streams. The soft jelly-like endocardium can only extend into the neutral zone between the spiraling streams and by its condensation provide the spiral aortico-pulmonary septum which divides the future pulmonary artery from the aorta. Any failure of the right heart to elongate sufficiently rapidly will distort the angle of approach of the two streams, thus producing a clockwise spiral which leads to transposition. Other changes in the angle of approach of the streams will cause the column of blood to fuse, resulting in persistence of the truncus arteriosus or, depending on its degree, to various types of over-riding of the aorta. Dynamic factors associated with slight retardation in the development of the heart itself are capable of modifying the arrangement of the vessels themselves.

This is evidenced by a case of twins suffering from congenital cardiac lesions, both of whom came under the care of Dr. Ann Purdy of this city, to whom I am indebted for details. The first twin died at three months, exhibiting at autopsy (1) an interventricular septal defect of the pars membranacea; (2) a closed ductus arteriosus; (3) complete transposition of the great vessels; (4) normal atria and veins. The second of the twins succumbed at eighteen months and at autopsy the heart showed (1) an interventricular septal defect of the pars membranacea; (2) a huge patent ductus arteriosus; (3) a normal arrangement of the great vessels; (4) normal atria and veins. The importance of this case rests upon the fact that the twins were "identical," uniovular and homozygous, with but a single placenta, and therefore were of identical genetic constitution. Yet the vascular anomalies differed markedly and the only finding in common was an interventricular septal defect.

It is by no means presumptuous to assume that the identical twins were subjected in utero to the identical noxious factor acting at the identical chronological time and in the identical amount, which has resulted in greatly different anomalies from subtle differences in degree of embryonic injury and of timing. The vascular lesions themselves reflect slight differences in the dynamic factors which are not difficult to envisage. Among the subtle factors at work in creating these differences are those which determine the biological age of the individual as distinct from his chronological age. Anyone who has engaged in the mensuration of uniovular homozygous twins in the embryonic, fetal or post-fetal stage is aware of the differences between them. One member of the pair may exhibit features the equivalent of an eight-week embryo, whereas the other member, as judged by linear dimension and other criteria, may be only the

equivalent of a six- or seven-week embryo. These differences are due not only to the amount of placenta, and therefore of nutrition, which each member appropriates to itself, but also to the ratio of change occurring in various metabolic processes within the embryo or fetus itself and which may be designated generally as maturation. Sidereal or chronological time has reference to the movement of the sun, the moon and other astral bodies; biological time to internal metabolic processes. This is a concept of great practical importance for the understanding of developmental and growth processes. The principles have been employed with great effectiveness by Abbott and myself[30] for such matters as the accurate prediction of the growth of the femur and tibia in leg shortening or lengthening operations.

In its earlier history, the pursuit of the individual to obtain understanding of his nature and his being has written one of the most curious chapters in medicine and biology. It gave us the raft of pseudo-sciences, such as physiognomy, chiromancy, neomancy (divination by observation of the moles and warts on the body), phrenology and many others, which float in a sea of superstition, supernaturalism and charlatanism. William Lessa[31] points out that these precursors of the science of human constitution, which he calls "somatomancy," contained a germ of truth leading to the legitimate modern science of human constitution, or "biotypology," as it is sometimes called. Unhappily, attempts to determine the morphogenotype of an individual, as by Sheldon's methods, are highly subjective, with few operational referents so that Washburn[32] could caustically conclude that the "system has its roots in characterology, not science, and is 'the new Phrenology in which the bumps of the buttocks take the place of the bumps of the skull'." Be these critics as they may, the error would seem to rest with the too ready assumption that individual morphological variation *necessarily* reflects physiological and functional differences in the individual.

A study of development, individual variation and developmental defects, whether experimentally or naturally caused, makes us doubt that much insight into the physiological processes of the individual is to be gained by study of outward physical constitution. Nevertheless a study of the individual clearly differentiates between genetic factors determining individual characteristics, as distinct from factors of metabolism which enable the individual to achieve his individual physical potentiality. It may be said that the genes sketch the plan of the future individual in a light pencil drawing; the organizers, regulation and other factors of embryonic development ink in the blue print; and nutritional and metabolic agents complete the building to a greater or less extent, depending upon external interruptions. Consequently we recognize that the overwhelming majority of congenital deformities are *not* genetically determined. The assumption that such deformities and variations seen in man are mutants is unproved and unwarranted: a fact which should be borne in mind in this period of hysteria over radioactive fallout. The extrapolation made in regard to the somatic effects of radiation depending upon statistics of congenital defect are most unreliable for the reason that the mechanisms are largely unknown and the almost universal failure to appreciate that most defects and

malformations in children are not mutations. Furthermore, with respect to congenital deformities, we should not adopt a position of therapeutic nihilism but recognize that preventive measures are a distinct possibility.

We are on the threshold of understanding biochemical and enzymatic factors. The existing evidence suggests a rich reward to those who would pursue this field as already shown by Beadle in his study on the biochemistry of the gene. Certain it is that we need to refine our parameters in applying chemical tests to the individual.

A more vigorous study of human individuality extending beyond the behavioristic and the psychological, to man's physiological and biochemical constitution is greatly needed and may lead, perhaps, to a newer, richer, Hippocratic medicine of the individual in the forthcoming age.

References will appear in author's reprints.

A Secure and Adjustable Support for Thoracentesis

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Positioning and supporting patients for thoracentesis in a sitting posture either in a hospital bed or on a treatment table frequently leaves the patient in an insecure attitude and the operator in an awkward position.

If the patient is placed on the edge of a bed, his dangling legs present a problem that is solved most often by an improvised placement of a chair or a stool as a foot rest. Support for the shoulders, which most sick patients require, is provided usually by a nurse or attendant who is thus immobilized and unable to render further assistance. The operator must lean across the bed to reach the patient's back. This is especially awkward when explorations with the thoracentesis needle must be made through the lateral chest wall.

A sturdy and adjustable support that can be constructed in any hospital maintenance shop is illustrated in Figures 1 and 2. The broad base slips readily under a hospital bed or operating table. The large table top, 15

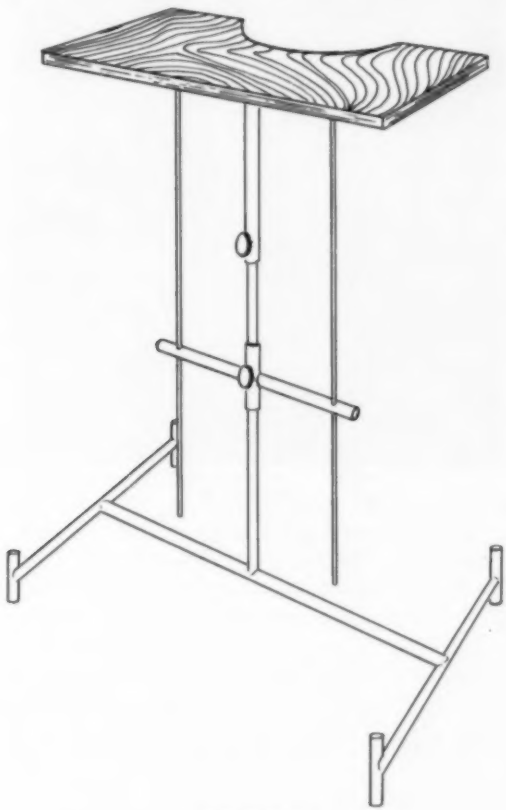

FIGURE 1

inches by 30 inches, provides a solid and comfortable rest for the elbows and forearms, giving the patient a gratifying sense of security; in addition, this position elevates the scapulae.

The height of the table top and the height of the foot bar are adjustable and held in place by heavy set screws with large knobs to fit the palm of the hand. Height range of the top is 43 inches to 53 inches.

A semi-ellipse, five inches by 15 inches, is cut from the edge of the table top toward the patient. The top is fastened eccentrically on the upright to allow adequate extension over the bed; this allows the patient to sit well back on the bed or table and adds to his sense of security.

Once the patient is positioned against the support, the nurse or attendant is free to assist the operator.

FIGURE 2

SECTION ON CARDIOVASCULAR DISEASES

The Effect of Exercise on Left to Right Shunt of Blood Through a Ventricular Septal Defect

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The effect of exercise on the pulmonary circulation has been studied in normal patients, but hemodynamic changes which occur with exercise in patients with acyanotic congenital heart disease associated with a left to right shunt have not been adequately studied.

A left to right intracardiac shunt is well shown by dye dilution techniques.[1] The contour of the curve obtained on the degree of shunting, and a measure of this is the ratio of built-up (BT) : disappearance time (DT). When this is above 1:2-2.1 a left to right shunt is present, as shown by Broadbent et al,[2] and this has also been our experience. As the degree of shunting increases, the BT:DT ratio decreases. The ratio is often expressed DT:BT, when this will increase with shunting. For qualitative clinical purposes the former representation has proven simpler and will be used. Changes in left to right shunt with exercise were studied by comparing dye dilution curves done on patients at rest and when exercising. The results were interpreted in relation to pressures recorded during cardiac catheterization.

Method

The tests were done with the patient in the supine position. A direct writing oximeter, a modification of the Millikan ear oximeter[3] was fitted on the left ear, and 100 per cent oxygen administered for 5 minutes before the injection of dye. Evans Blue dye (T 1824) in dosage of 0.2 mgm. per Kg. body weight was injected rapidly into a right antecubital vein.[4] Care was taken to avoid any constriction above the site of injection.

The patient exercised in the recumbent position by moving a pair of roller skates up and down inclined wooden ramps for a minimum of 4 minutes. The slope of the ramps and the weights attached to the skates were varied to suit the strength of the patient. The same amount of dye was again injected during the period of exercise. The amount of work done varied widely, depending on the strength of the patient, but averaged 1.7 ft. lbs./sec. (range from 1.2-2.4).

A normal dye dilution curve is demonstrated by Figure 1, and a typical left to right shunt by Figure 2.

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TABLE I—MEASUREMENTS FROM DYE DILUTION CURVES RECORDED AT REST AND DURING EXERCISE ON 9 PATIENTS WITH VENTRICULAR SEPTAL DEFECT

Patient	At Rest A.T.	B.T. Secs.	D.T.	Ratio B.T.:D.T.	Exercising A.T.	B.T. Secs.	D.T.	Ratio B.T.:D.T.
Case 1 (MB)	8.8	9.8	27.5	1:2.8	8.4	7.5	17.1	1:2.3
Case 2 (RB)	5.9	14.6	40.0	1:2.8	4.8	11.0	21.6	1:2
Case 3 (DB)	8.8	10.0	47.3	1:4.7	10.0	8.5	34.4	1:4
Case 4 (SC)	5.9	13.8	47.5	1:3.4	5.9	9.0	17.8	1:2
Case 5 (DBn)	7.0	7.6	14.1	1:1.9	6.5	12.5	31.1	1:2.5
Case 6 (GF)	9.0	7.4	19.0	1:2.6	7.3	10.0	large	large
Case 7 (JW)	10.6	11.8	25.0	1:2.1	9.4	12.5	41.1	1:3.3
Case 8 (PC)	6.0	12.1	16.7	1:1.4	4.3	12.0	17.5	1:1.5
Case 9 (CB)	(1) 9.5	9.4	28.5	1:3	7.4	7.2	13.0	1:1.8
	(2) 7.0	7.0	14.5	1:2.1	7.1	9.2	22.5	1:2.4

A.T.—Appearance time. B.T.—Build-up time. D.T.—Disappearance time.

Nine patients with interventricular septal defects were old enough to cooperate and were considered representative of a large number of patients in this group. The method of exercise described was acceptable to children over five to six years. The dye dilution curves were done with the patient awake and somewhat apprehensive. It was not possible to record intracardiac pressures at rest and exercise because of the sedation necessary during the cardiac catheterization of young children. Therefore, the pressures were obtained under basal conditions.

Results

The results of the dye dilution curves are given in Table I. It will be noted that in the four cases the ratio of BT:DT increases with exercise. In Cases 5, 6 and 7 this ratio diminishes with exercise.

In Table II the pressures obtained at cardiac catheterization are recorded and may be compared with the change in ratio of BT:DT caused by exercise.

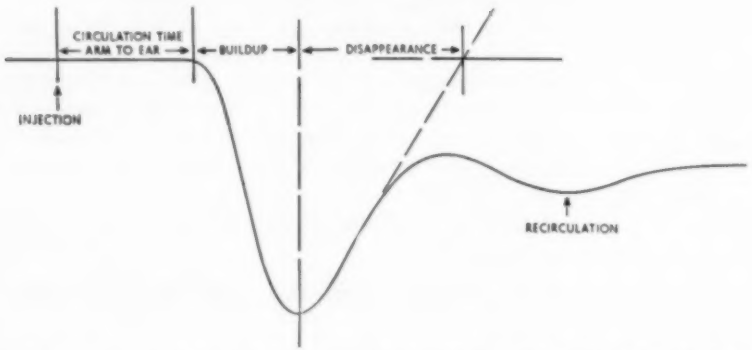

FIGURE 1: A normal dye dilution curve. Appearance time is the arm to ear circulation time.

TABLE II—RESULTS FROM DYE DILUTION CURVES AND CARDIAC CATHETERIZATION DONE ON NINE PATIENTS WITH VENTRICULAR SEPTAL DEFECT

	Ratio of B.T.:D.T. At Rest	Exercising	Cardiac Catherization Pressures mm. Hg.	
Decrease in Left to Right Shunt With Exercise				
1. Patients with pulmonary hypertension				
Case 1 (MB)	1:2.8	1:2.3	R.A.	10/3
			R.V.	100/0
			P.A.	100/50
Case 2 (RB)	1:2.8	1:2	R.V.	60-65/0
			at V.S.D.	90/0
			P.A.	55-60/20
2. Patients with pulmonary stenosis				
Case 3 (DB)	1:4.7	1:4	R.A.	4/0
			R.V.	52/0
			P.A.	25/4
Case 4 (SC)	1:3.4	1:2	R.A.	8/2
			R.V.	45/0
			P.A.	30/10
Increase in Left to Right Shunt With Exercise				
Case 5 (DBn)	1:1.9	1:2.5	R.V.	27/0
			P.A.	27/10
Case 6 (GF)	1:2.6	Large	R.A.	5/2
			R.V.	30/0-6
			P.A.	30/12
Case 7 (JW)	1:2.1	1:3.3	R.A.	8/5
			R.V.	50/5
			P.A.	55/25
Special Cases				
Case 8 (PC)	1:1.4	1:1.5	R.A.	3/0
			R.V.	100/0
			P.A.	100/55
Case 9 (CB)	(1)1:3	1:1.8	R.A.	5/2
	(2)1:2.1	1:2.4	R.V.	20/0
			P.A.	18/4

B.T.—Build-up time. D.T.—Disappearance time. R.A.—Right atrium.
R.V.—Right ventricle. V.S.D.—Ventricular septal defect. P.A.—Pulmonary artery.

Case 1 (Figure 3) had a ventricular septal defect, persistent left superior vena cava and pulmonary hypertension. Case 2 had a ventricular septal defect, anomalous pulmonary vein entering the superior vena cava, and moderate pulmonary hypertension. It was considered that these anomalous vessels would not cause the diminution in left to right shunt associated with exercise. Cases 3 and 4 (Figure 4) had ventricular septal defects and pulmonary stenosis, as shown by the catheterization data. These four patients diminished their left to right shunt with exercise. Two subjects (Cases 2 and 4) who had left to right shunt at rest, had normal dye dilution curves when exercising.

Decrease in BT:DT ratio with exercise occurred in Cases 5, 6 (Figure 5) and 7. Cases 5 and 6 had normal right ventricle and pulmonary artery pressures, while Case 7 had moderate pulmonary hypertension.

Case 8 (Figure 6) had equal right ventricle, pulmonary artery and brachial artery (cuff method) blood pressures although at cardiac catheterization the blood samples taken demonstrated a left to right shunt at the ventricular level. However, when awake, both at rest and when exercising,

there was no flow of blood through the septal defect as shown by the normal dye dilution curves.

Case 9 had normal right ventricle and pulmonary artery pressures at cardiac catheterization. Figure 7 shows the dye dilution curves on two separate occasions. The first curve was obtained with the patient relaxed and at rest. It reveals a left to right shunt. The second curve recorded when exercising demonstrates an increase in the ratio of BT:DT. Although the patient was exercising well no rise in arm blood pressure occurred. At the second visit the patient was more apprehensive, and the curve at rest was similar to that when exercising previously.[5] He then exercised hard and elevated the arm blood pressure from 110/60 to 120/70 mms. Hg. The dye dilution curve recorded at this time indicates a decrease in the BT:DT ratio as compared to the ratio in the curve taken at rest.

Discussion

There are various reports of data obtained at cardiac catheterization in normal persons both at rest and during exercise. Hickam and Cargill[6] who exercised 8 normal patients in the supine position, found no rise in pulmonary artery pressure with light exercise. Riley and co-workers[7] catheterized three normal subjects, who then exercised sitting up. A fall in pulmonary and systemic resistance was found in all, while the pulmonary artery pressure fell in two and rose slightly in the third. The brachial artery pressure rose. Dexter and associates[8] recorded their data in 7 patients, in the recumbent position. The brachial artery and pulmonary artery rose in all, in the latter an average of 8.5 mms. Hg. The pulmonary resistance was found to rise in all but a few during moderate exercise, while the systemic resistance fell. The findings of Donald and co-workers[9] in 16 normal subjects who exercised in the recumbent position, demonstrate a rise in pulmonary artery pressure averaging 8 mm. Hg. in all but one patient. There was little rise in brachial artery pressure on light exercise, but it became greater with heavy exercise, and was then accompanied by a larger fall in systemic resistance. The pulmonary arteriolar resistance in general showed a slight rise, being more marked in light than heavy exercise. Sancetta and Rakita[10] in 12 subjects in the recumbent position, found a reduction in pulmonary resistance and a

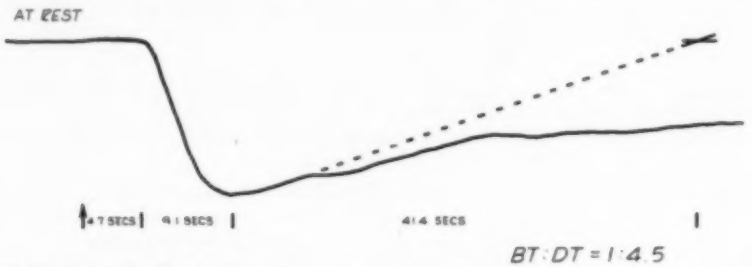

FIGURE 2: A typical left to right shunt dye dilution curve, in a patient with a ventricular septal defect.

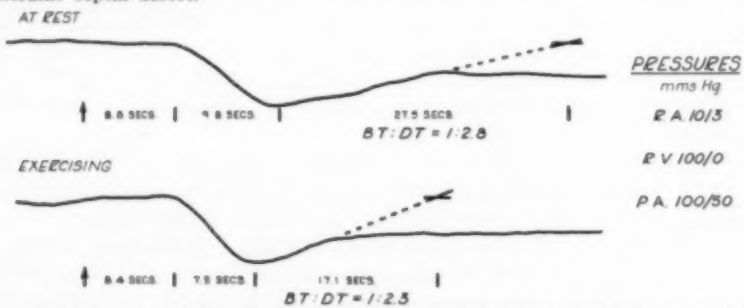

FIGURE 3 *(Case 1) (MB):* Dye dilution curves taken at rest and exercise, and pressures from cardiac catheterization. The ratio of BT:DT increases with exercise.

rise in pulmonary artery pressure which was followed by a fall after nine minutes exercise. Connolly and Wood[11] refer to data on nine healthy men. Exercise in the horizontal position caused a rise in pulmonary artery pressure averaging 10 mms. Hg. systolic, and in radial artery pressure of 29 mms. systolic. Cournand[12] found no rise in the pulmonary artery pressure until the blood flow was 3 times that at rest.

To summarize, normal patients in the recumbent position show a slight rise a pulmonary artery pressure with exercise. The pulmonary resistance has variously been recorded as falling or rising slightly, while the systemic resistance always falls. Systemic pressure, though it may not rise during light exercise is raised by moderate or heavy exercise.

Swan, Marshall and Wood[13] studied 13 patients with a left to right shunt. They found that with exercise this shunt diminished in all cases, but particularly in patients with pulmonary hypertension. Patients with equal aortic and pulmonary artery pressures had on exercising a further rise in pulmonary artery pressure, and no significant change in pulmonary resistance. Patients with pulmonary artery pressure below 50 mms. Hg. at rest showed no significant change in pulmonary pressure or resistance with exercise.

Flow of blood through a ventricular septal defect is proportional to the pressure gradient between the two ventricles, and inversely proportional to the resistance offered by the size of the septal defect, the latter being constant in any given patient.[14] Flow from the ventricles depends on the peripheral resistance and ventricular pressure.[15-19]

Patients with pulmonary hypertension diminished their left to right shunt with exercise. The rise in right ventricle pressure associated with the rise in left ventricle pressure will not cause an increase, and may result in a decrease in the interventricular pressure gradient. At the same time the fall in systemic resistance as compared to no alteration in pulmonary resistance will favor the flow of blood to the body and result in a diminution in left to right shunt.

When pulmonary stenosis is present the resistance at the pulmonary valve is a constant factor, and it would seem probable that with an increased cardiac output the right ventricle pressure will rise. Thus the effect is the same in pulmonary hypertension.

Case 8 had pulmonary hypertension of a degree at which flow through the right and left heart was balanced, and no shunting occurred.

An increase in left to right shunt on exercise was found in patients with ventricular septal defect who had normal or little raised pulmonary artery and right ventricle pressures. No, or minimal, rise in pulmonary artery pressure with exercise would be expected under these circumstances, so that with increased systemic pressure an

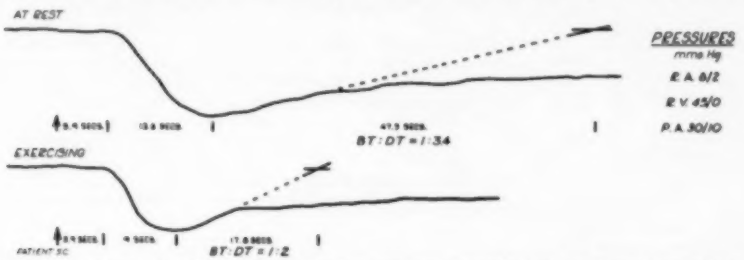

FIGURE 4 *(Case 4) (SC):* Dye dilution curves recorded at rest and exercise, and pressures from cardiac catheterization. The ratio of BT:DT increases with exercise.

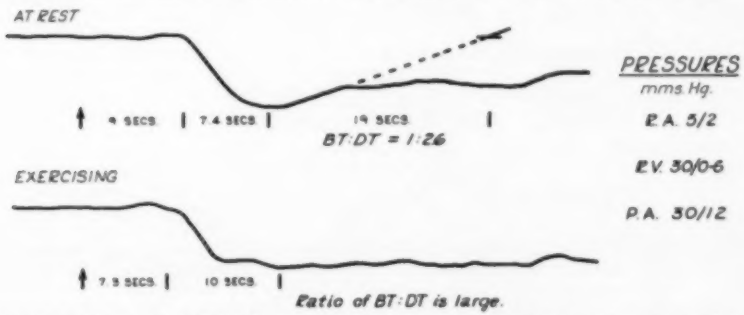

FIGURE 5 *(Case 6) (GF):* Dye dilutions curves recorded at rest and exercise, and pressures from cardiac catheterization. The ratio BT:DT decreases with exercise.

increase in the interventricular pressure gradient will occur. This will increase a left to right shunt. That the factor found in patients with pulmonary hypertension, namely a diminution in systemic as compared to pulmonary resistance was still acting, was suggested by Case 9. On the first occasion when no rise in systemic blood pressure was measured on exercise, only the second factor above was present, and resulted in the decrease in shunt as shown. At the second visit when an increase in arm blood pressure occurred, the increase in left to right shunt may be explained by the rise in interventricular pressure gradient.

There are not sufficient cases in this report to show at what level this change in response to exercise, demonstrated by the dye dilution curves, does occur. Excluding

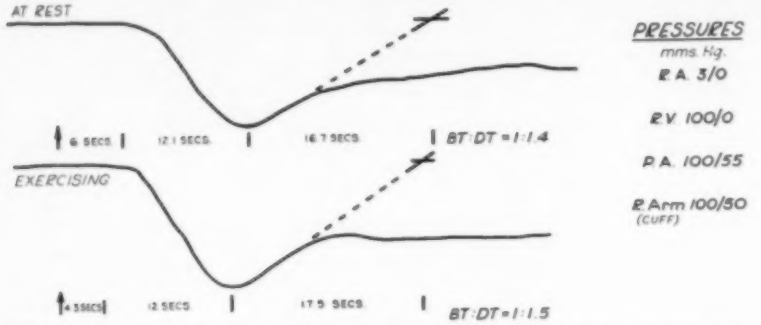

FIGURE 6 *(Case 8) (PC):* Dye dilution curves recorded at rest and exercise, and pressures from cardiac catheterization. There is no left to right shunt at rest or exercise.

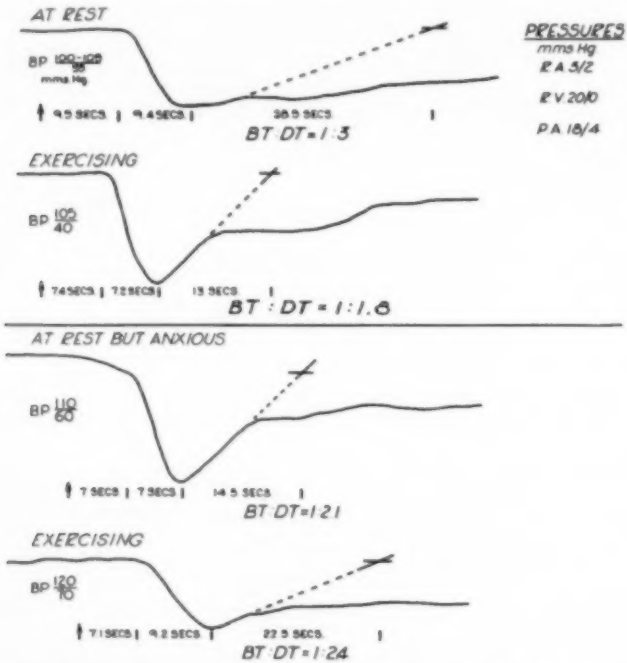

FIGURE 7 *(Case 9) (CB):* Dye dilution curves recorded at rest and exercise, and pressures from cardiac catheterization. These four curves are all from the same patient. The upper two recorded on one occasion show an increase in ratio of BT:DT with exercise, and no change in blood pressure. (Taken with a cuff on the left arm.) The lower recorded on another day show a diminution in ratio of BT:DT, together with a rise in blood pressure on exercise.

the patients with pulmonary stenosis, the lowest right ventricle pressure in a patient who decreased the left to right shunt by exercising is 60/0 mms. Hg. The highest right ventricle pressure in a patient increasing the shunt is 50/5 mms. Hg. This suggests a change at a right ventricle pressure of 50 to 60 mms. Hg.

The flow of blood through a ventricular septal defect has been demonstrated as a changeable hemodynamic situation. The effect of exercise varied from patient to patient. In some cases a decrease in left to right shunt occurred on exertion, in others an increase, in one no shunt of blood occurred through a known septal defect, while in a patient such as Case 9 the shunt may decrease or increase depending on the response of the systemic pressure to exercise. The other possibility, a reversal of left to right flow on exertion was not demonstrated in this group of patients.

SUMMARY

The effect of exercise on left to right shunt of blood through a ventricular septal defect has been studied.

Patients with ventricular septal defect and normal right ventricle and pulmonary artery pressures who raised their systemic blood pressure by exercise, showed an increase in the left to right shunt.

It is suggested that this increase in shunt is due to a rise in the interventricular pressure gradient.

In patients with ventricular septal defect and pulmonary hypertension or stenosis, a decrease in left to right shunt occurred with exercise.

This decrease is explained by a fall in systemic resistance with exercise, as compared to pulmonary resistance, while little change or perhaps a diminution in the interventricular pressure gradient occurred.

It is suggested that this technique makes it possible to study the natural history of the left to right shunt in patients with interventricular septal defects and to anticipate the development of frank pulmonary hypertension by repeated tests at necessary or even frequent intervals.

RESUMEN

Se estudió el efecto del ejercicio sobre la intercomunicación de izquierda a derecha en el defecto septal.

Los enfernos con defecto ventricular del septum y con ventrículo derecho normal y presiones pulmonares que ascendieron y produjeron ascenso de la presión arterial general por el ejercicio, mostraron un aumento de la intercomunicación de izquierda a derecha.

Se sugiere que este aumento del pasc se debe al aumento del gradiente de la presión de la presión interventricular.

En los enfermos con defecto interventricular e hipertensión pulmonar o estenosis, ocurrió el descenso en el paso de izquierda a derecha después del ejercicio.

Este decrec'miento se explica por la caída de la resistencia de la circulatión general con el ejercicio, en comparación con la resistencia pulmonar, en tanto que se observa poco cambio o probablemente una disminución interventricular.

Se sugiere que esta técnica hace posible estudiar la historia natural de la intercomunicación de izquierda a derecha en persona con defectos interventriculares y prever el desarrollo de hipertensión pulmonar franca pruedas a los necesarios o aún a intervalos frecuentes.

RESUME

Les auteurls ont étudié l'effet de l'exercice sur le shunt du courant sanguin de gauche à droite, à travers une altération de la paroi ventriculaire.

Les malades atteints d'une malformation de la paroi ventriculaire, avec des pressions normales du ventricule droit et de l'artère pulmonaire qui avaient élevé leur pression sanguine générale par l'exercice, montrèrent une augmentation du shunt de gauche à droite.

Il est suggéré que cette augmentation du shunt est dû à une élévation du degré de la pression interventriculaire.

Chez les malades atteints d'altération de la paroi ventriculaire avec hypertension pulmonaire ou sténose, une diminution du shunt de gauche à droite survint après exercice.

Cette diminution est expliquée par une shute de la résistance générale après exercice, qu'on peut comparer à la résistance pulmonaire, tandis qu'une petite modification ou peut-être une diminution survint dans le degré de la pression interventriculaire.

Les auteurs suggèrent que ce procédé puisse rendre possible l'étude de la connaissance du shunt de gauche à droite chez les malades atteints d'altérations de la paroi interventriculaire et la prévision du développement d'une hypertension pulmonaire franche par des tests répétés quand 'ecst nécessaire ou même à de fréquents intervalles.

ZUSAMMENFASSUNGEN

Es wurde die Auswirkung einer Belastung auf den Links-Rechts-Shunt des Blutes durch einen Kammerscheidewand-Defekt untersucht. Kranke mit Kammerscheidewand-

Defekt und normalen Druckwerten im rechten Ventrikel und der art.pulm., deren peripherer Blutdruck nach Belastung anstieg, zeigten eine Zunahme der Links-Rechts-Shunts.

Es wird die Vermutung ausgesprochen, dass die Zunahme des Shunts die Folge einer Erhöhung des interventrikulären Druckgefälles darstellt.

Bei Kranken mit Kammerscheidewand-Defekten und pulmonalem Hochdruck oder Stenose kommt bei Belastung es zu einer Abnahme des Links-Rechts-Shunts.

Diese Abnahme lässt sich erklären als ein Abfall des Widerstandes im Körper während der Belastung im Vergleich zu dem Widerstand in den Lungen, während nur eine geringe Veränderung oder vielleicht eine Verringerung des interventrikulären Druckgefälles eintritt. Es wird angenommen, dass es diese Technik ermöglicht das natürliche Verhalten des Links-Rechts-Shunts zu prüfen bei Kranken mit interventrikulären Scheidewanddefekten und durch wiederholte Teste in gegebenen oder auch häufigen Intervallen die Entwicklung einer offenen pulmonalen Hypertension im voraus zu bestimmen.

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The Importance of the Myocardial Factor in the Surgical Treatment of Rheumatic Aortic Stenosis

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Although major advances in the field of medicine and surgery frequently develop with astonishing rapidity, painstaking years of research usually precede the final achievement. Subsequently, a good deal of time must be spent to elucidate those factors which in some way might influence the attainment of an ideal clinical result.

The development of techniques for the surgical treatment of aortic stenosis adheres to this general pattern. The continued interest in these methods is explicable on the basis of the generally satisfactory results obtained by aortic commissurotomy. It also necessitates detailed inquiry into other facets of this important problem.

Preliminary steps along these lines have been made. One review[1] outlined the importance of aortic valve calcification and leaflet mobility in patients undergoing commissurotomy while another study[2] considered the prognostic importance of left bundle branch block in a smaller group of cases.

The present article indicates the importance of the myocardial factor in the treatment of rheumatic aortic stenosis by summarizing our experiences with patients who had considerable left ventricular enlargement and who were subjected to operation.

Methods and Material

The records, including roentgenograms, of 196 patients who had an aortic commissurotomy performed during the interval from April, 1952 until July, 1956 were reviewed. Of these, 26 cases were selected for the present study. All in this group had radiographic evidence of massive left ventricular enlargement (3 plus or greater, based on a range of 0 to 4 plus). In appraising heart size, the important factors of body weight, height, surface area, age, and sex were considered. It was recognized that there are objections to all forms of cardiac measurement especially when studies are made in only one dimension.

Each patient had major aortic stenosis alone or in combination with an insignificant degree of aortic regurgitation. Eleven were operated on by the transventricular and 14 by the transaortic approach. One had an aortic commissurotomy performed by an open technique employing circulatory by-pass and controlled cardiac arrest.

Preoperatively, right heart catheterization was performed in eight cases and it was repeated postoperatively in two. Combined heart catheteriza-

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tion was carried out before and after surgery in one case according to techniques previously described.[3]

Results

1. Hospital Course:

Of the 11 patients operated on by the transventricular approach, three (27 per cent) died at the time of operation or in the immediate postoperative period. There were 4 (28 per cent) hospital deaths among the 14 subjected to transaortic commissurotomy. One survived open heart surgery.

Cardiac arrest or ventricular fibrillation accounted for four of the deaths at the time of surgery. In one case ventricular standstill was precipitated by the inadvertent technical mishap in which a coronary vessel was injured. Miscellaneous causes of death included heart failure, subacute bacterial endocarditis, and the production of dynamic aortic regurgitation.

2. Follow up Review:

There were six (60 per cent) late deaths in the follow-up group of patients operated on by the transaortic approach during an interval extending up to four years after surgery. Five of these were due to cardiac failure while one was presumably the result of cardiac arrest.

There were six (75 per cent) late deaths in the group operated by the transventricular approach during an interval extending up to four and one-half years after surgery. Half of these were due to heart failure while the remainder were due to unknown causes or cardiac arrest.

Of the late deaths seven occurred within one year following the aortic commissurotomy.

A total of seven surviving patients have been followed for a period extending from six months to four years. All of these patients were clinically improved.

The total mortality rate (hospital and late deaths) for all patients operated on for aortic stenosis with massive left ventricles was 73 per cent.

Discussion

In early stages of aortic stenosis a greater stroke output is accomplished by the combination of a more forceful myocardial contraction and a more prolonged systolic ejection period. With greater degrees of stenosis, the systolic pressure generated by the left heart muscle must exceed that in the central aorta to insure an adequate cardiac output. The presence of this chronic pressure load leads to myocardial hypertrophy. The myocardial fibers must increase in size in order to generate the tension needed to produce high intraventricular pressures. In the advanced stages of the disease dilatation becomes relatively more significant as the left ventricular chamber becomes massive in size.

The dynamic properties of heart muscle are not completely understood[4-6] although important advances have been made. Most agree, however, that the larger the heart, the less its mechanical efficiency and the less the ability to perform useful work.[7]

An enlarged heart may be associated with specific chemical imbalances. These may take the form of deficiencies in metabolites needed to produce high energy phosphate as well as the muscle protein needed for contraction.[8]

It is readily apparent that there is no exact correlation between the degree of load placed on a heart chamber and the extent of the cardiac enlargement that results. In a series of patients with rheumatic aortic stenosis who have undergone combined cardiac catheterization, markedly narrowed aortic valve areas were noted in patients with both small and large hearts.[9]

One of the known limiting factors in cardiac hypertrophy appears to be the coronary vascular bed, which remains unchanged in the face of an increased muscle mass.[10] The difficulty in perfusing these vessels becomes more important in aortic stenosis where special hemodynamic situations prevail. Left heart catheterization studies have shown a tendency for elevation of the diastolic pressure in patients with far advanced aortic

stenosis in the absence of congestive heart failure. This has been related to the pressure-volume relations of the left heart chamber.[11] This factor, combined with the lengthening of the duration of systolic ejection, diminishes the period of diastole with consequent impairment of coronary perfusion. While most of the coronary flow occurs in diastole, some takes place during systole.[12] This flow is seriously interfered with in aortic stenosis. The perfusing pressure on the aortic side of the valve is diminished, while the high intraventricular pressure decreases flow by limiting venous drainage. It is also possible that the abrupt change in flow across the stenosis orifice causes a fall in lateral pressure with production of a Venturi effect, limiting coronary filling.[13] The failure of the myocardium in aortic stenosis then may be considered the direct result of coronary insufficiency.

Attempts to define this myocardial factor, non-specific and variable as it is, have been made by two groups. Hecht,[13] in a review of patients with chronic cor pulmonale, noted that patients with chronic lung disease and pulmonary hypertension develop congestive heart failure only with advancing years. In such cases it is apparent that at least one factor, coronary atherosclerosis, determines how well the myocardium can tolerate the added load produced by elevation of pressure within the pulmonary circuit.

In rheumatic heart disease Harvey et al.[14] have studied a special aspect of this myocardial factor. They observed a small group of patients with mitral stenosis, who, in the absence of clinical failure, had little or no pulmonary hypertension at rest. Yet, there was no appreciable increase in cardiac output on exercise. More than half of this group had low cardiac outputs at rest. They concluded that these patients had low cardial output due to myocardial insufficiency rather than mechanical block. It was their impression that the performance of a mitral commissurotomy is of little value in these patients.

On the other hand, Dickens and her associates employing the technique of combined heart catheterization, noted widely varying degrees of pulmonary hypertension and cardial output in patients with similar mitral valve areas.[3] They interpreted their data as indicating little upon which to predict the result of the surgery.

In our group of cases with aortic stenosis and massive cardiac enlargement, right heart catheterization proved of little value in the identification of a common physiological substrate. The resting cardiac index was below normal in five of the eight cases and ranged from 1.8 to 2.9 L/M^2 B.S.A. The pulmonary artery pressures were elevated

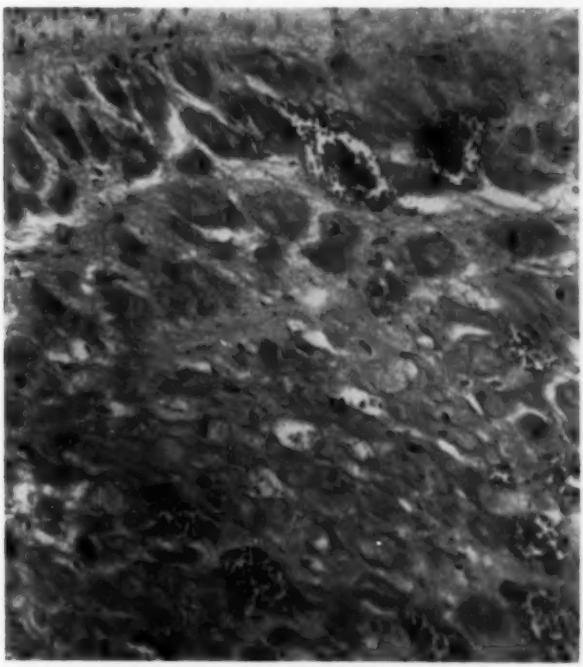

FIGURE 1: Photomicrograph magnified to demonstrate an area of necrosis in left ventricle of a patient with massive hypertrophy. Note secondary vascular and fibroblastic proliferation. The left coronary vessel showed minimal arteriosclerosis.

TABLE I—RELATION OF HEART SIZE TO MORTALITY RATE IN AORTIC COMMISSUROTOMY

Heart Size	Number of Cases		Operative		Late		Total	
	Total	Follow-up	Deaths	Per cent	Deaths	Per cent	Deaths	Per cent
0 - 2 plus	170	170	36	21	31	23	67	39
3 plus - 4 plus	26	26	7	26	12	63	19	73

in three, and in one patient with repeated bouts of left heart failure it was recorded at 110 mm. of Hg. (systolic).

Two of these cases were studied postoperatively and, in one, the resting cardiac index rose by 50 per cent.

In the one patient studied before and after surgery by combined heart catheterization, the systolic ejection gradient across the aortic valve was eliminated completely. This observation strongly suggests that satisfactory objective alterations can be accomplished even in the presence of significant cardiac enlargement.

Post-mortem examination was obtained in a few cases. The pathological changes in the heart muscle itself were not specific. Scattered areas of fibrosis were common, and focal necrosis and myomalacia were occasionally demonstrated (Fig. 1). The incidence of coronary artery disease did not appear to be increased. When present, it often precipitated an accelerated devolutionary phase of the disease.

With knowledge of the detrimental effects of massive ventricular hypertrophy, it was interesting to note the negligible difference in mortality rate between those operated on by the transaortic approach and those subjected to transventricular aortic commissurotomy. In addition, the mortality rate in larger series of 170 patients with smaller (0-2 plus) hearts was only slightly less than in the group with massive left ventricles. (Table I).*

While patients with large hearts tolerated cardiac surgery almost as well as the control group, they generally did poorly postoperatively. Nearly six out of 10 were dead within five years and 68 per cent expired within 12 months after aortic commissurotomy. On the other hand in the follow-up group of 134 patients with smaller hearts only two out of 10 had died within a comparable period of time.

The total mortality rate (hospital and late deaths) was two times greater in patients with massive left ventricles.

Despite the fact that an occasional patient in this special group did improve after aortic commissurotomy, it seems best to consider patients with massive left ventricles as poor candidates for aortic commissurotomy. It is recognized that mistaken evaluations will still be made in the absence of specialized diagnostic procedures capable of identifying and approximating the severity of the myocardial factor. A study of left ventricular hemodynamic data in patients of this type is now in progress. Also, this analysis may not hold in cases where aortic commissurotomy is carried out by an open technique.

CONCLUSIONS

1. The importance of the "myocardial factor" is considered in a review of 26 patients with massive left ventricular hypertrophy undergoing aortic commissurotomy.

2. The hospital mortality rate was 28 per cent despite the closed technique employed. This was slightly higher than the mortality rate of 21 per cent in a group of 170 patients with aortic stenosis and small left ventricles.

3. A follow up of 19 cases who survived surgery revealed that 63 per cent had expired as compared to 23 per cent in a group of 134 cases with small left ventricles. The total mortality was 73 per cent in those with massive left ventricles as compared to 39 per cent in the control group.

4. The various limiting factors in cardiac hypertrophy are discussed, and the cardiac catheterization data in nine patients is reviewed. In one case studied by left heart catheterization a significant drop in the systolic gradient across the aortic valve was recorded.

5. It is concluded that this group generally represents poor candidates for the performance of an aortic commissurotomy, especially if a closed technique is employed.

CONCLUSIONES

1. La importancia del "factor miocárdico" se ha considerado en 26 enfermos con hipertrofia ventricular izquierda voluminosa que sufrieron la comisurotomía aórtica.

2. La mortalidad en el hospital fué de 28 por ciento a pesar de la técnica cerrada empleada. Esta fué ligeramente más alta que la mortalidad de 21 por ciento en un grupo de 170 enfermos con estenosis aórtica y pequeños ventrículos izquierdos.

3. El seguimiento de 19 casos de estenosis aórtica que sobrevivieron, reveló que el 63 por ciento habían muerto comparado con 23 por ciento del grupo de 134 vasos con ventrículos pequeños.

La mortalidad total fué 73 por ciento en los que tenían ventrículos izquierdo con gran hipertrofia comparada con 39 porciento del grupo de control.

4. Se discurre sobre los factores limitantes en el caso de hipertrofia cardiaca y se revisan los datos de la cateterización cardiaca en 9 casos. En un caso estudiado por cateterización del corazón izquierdo, se registró una caída significativa del gradiente sistólico a través de la válvula aórtica.

5. Se concluye que este grupo generalmente es de candidatos malos para la comisurotomía aórtica en particular si se emplea la técnica cerrada.

ZUSAMMENFASSUNGEN

1. Die Bedeutung des "Myocard-Factors" wird einer Analyse unterzogen in einer Übersicht von 26 Kranken mit starker links-seitiger Kammerhyperthrophie, die sich einer Aorten-Kommissurotomie unterzogen.

2. Die Ziffer für die Krankenhaussterblichkeit betrug 28% trotz der angewandten geschlossenen Technik. Sie war etwas höher als die Sterblichkeitsziffer von 21% bei einer Gruppe von 170 Kranken mit Aortenstenose und kleinen linken Kammern.

3. Eine Nachuntersuchung von 19 Fällen, die die Operation überlebten, ergab, dass 63% gestorben waren im Vergleich zu 23% in einer Gruppe von 134 Kranken mit kleinen linken Ventrikel. Die Gesamtmortalität betrug 73% bei solchen mit starken linken Kammern im Vergleich zu 39% in der Kontrollgruppe.

4. Die verschiedenen beschränkenden Faktoren bei der Herzhyperthrophie werden besprochen und die Werte bei Herzkatheterisierung von 9 Kranken durchgesehen. In einem Fall, der mittels Katheterisierung des linken Herzens untersucht worden war, war ein beträchtlicher Abfall im systolischen Druckgefälle quer durch die Aortenklappen zu verzeichnen.

5. Es wird gefolgert, dass diese Gruppe ein schlechteres Ausgangsmaterial bietet für die Vornahme einer Aorten-Kommissurotomie, besonders bei Verwendung der geschlossenen Technik.

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Myocardial Infarction, Its Diagnosis and Treatment: Literature Review*

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Myocardial infarction is a pathological process established by a compromise in the blood supply to an area of myocardium of such severity that even with prolonged rest adequate oxygen connot be obtained. In the United States there are approximately 600,000 to 800,000 persons each year suffering attacks from this disease.[1] Even though in recent years greater facilitation in diagnosis and tremendous strides in therapy have reduced mortality during the first attack in private patients to 5 per cent or less,[2] the overall annual mortality is 200,000.[1] A large number of the deaths occur during the most productive years of life; many of those who survive suffer disabling complications. The figures for mortality and disabling complications can be decreased by a careful differential diagnosis of patients presenting chest pains and other symptoms characteristic of myocardial infarction and by individualization of therapeutic procedures.

Diagnosis

The diagnosis of acute myocardial infarction is based on the history, the clinical findings, and an evaluation of the electrocardiographic changes. There are many nonspecific signs which may be used as adjuncts.

A tentative diagnosis of myocardial infarction may be suggested in a patient presenting a severe, oppressive pain over the lower sternum or more extensively over the precordium or anterior chest which lasts for 30 minutes or longer and which is not relieved by rest or nitrites.[3] Radiation of this pain to neck, shoulders, or arms confirms the likely origin in the heart. The pain builds up slowly and steadly to a plateau of maximal intensity. Anxiety and fear of impending doom mount rapidly as the pain continues. After several hours the pericardial inflammation resulting from ventricular necrosis may introduce a sharp, stabbing component to the pain. It is typically aggravated by respiration, emotion, swallowing, and may have a throbbing element synchronous with the heartbeat.[4] Complications as shock and congestion of the lungs from acute left ventricular failure may increase the complexity of the symptoms;[4] however, a rapid fall in blood pressure within twenty-four hours or even a more gradual fall in the next few days is interpreted as an important confirmatory sign.[3] Fever, leukocytosis, and elevation of the erythrocyte sedimentation rate are clinical signs which support the diagnosis.

Serial changes in the electrocardiogram are of great value, but not essential, for the diagnosis.[4] The electrocardiogram is considered characteristic of acute myocardial infarction when elevation of the RS-T segment and a deep Q wave are present in one or more leads, with progressive change from RS-T elevation to T-wave inversion in serial records.[5] At

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the onset of the attack the electrocardiogram may be normal or may show only slight changes.[2] At this time, RS-T depression may occur instead of the expected RS-T elevation, which may not appear for hours. The Q waves may appear even later, at the end of one or two days.

The diagnosis of myocardial infarction must be established by evidence of tissue deterioration.[4] This is done most often with studies on glutamic-oxalacetic transaminase, the infarcted muscle releasing two to twenty times the normal serum value within 24 hours, returning to normal three to seven days thereafter.[6] This test by itself is nonspecific because other body tissues release glutamic-oxalacetic transminase in disease, e.g., liver, kidney, pancreas, and skeletal muscle. It must be used in conjunction with the studies outlined above. Measurements of serum transaminase can be done in most well-equipped hospital and clinical laboratories, the procedures being reasonably standardized and the necessary reagents commercially available.

Included in the differential diagnosis of myocardial infarction should be the following diseases:[3]

1. Chest — angina pectoris
   acute coronary insufficiency
   pulmonary embolism
   cardiac arrhythmias
   acute pericarditis
   spontaneous pneumothorax
   dissecting (nonsyphilitic) aneurysm of the aorta
   spontaneous interstitial emphysema of the lung
   malingerers familiar with the symptoms of myocardial infarction
   other chest diseases —
      syphilitic aortitis with aortic aneurysm
      pneumonia
      pleurisy
      massive collapse of the lung
      carcinoma of the lung
      diaphragmatic or paraesophageal hernia
      herpes zoster
      costochondral arthritis
      rupture of the costochondral junction
      diseases of the spine or shoulder with referred pain to the anterior chest wall
2. Abdomen — acute indigestion
   acute surgical abdominal disease —
      perforated peptic ulcer
      cholelithiasis
      acute cholecystitis
      acute pancreatitis
      acute intestinal obstruction
      acute appendicitis
      biliary colic
      sigmoid spasm
      food poisoning
      tabetic crisis
      acute postoperative peritonitis
      renal or ureteral colic with reflex ileus and pain in abdomen or chest
3. Other clinical syndromes — diabetic coma
   sickle cell anemia during a hemolytic crisis
   Addison's disease during a crisis

These conditions differ from myocardial infarction in their electrocardiographic pattern.

TABLE I

A MOST IMPORTANT DIFFERENTIAL DIAGNOSIS IS OUTLINED AS FOLLOWS

	Angina Pectoris	Acute Coronary Insufficiency	Myocardial Infarction
Precipitating factors[3]	effort emotion trauma reflex from other viscera tobacco insulin adrenalin cold eating	similar to angina pectoris spontaneous acute conditions, with anoxemia hemorrhage shock or fall in B.P. sudden rise in B.P. tachycardia heart failure infections trauma operations anesthesia	at rest or during routine activity
Pain[3]	temporary relieved by nitro-glycerin	variable, often absent	prolonged not relieved by nitro-glycerin
Circulation[3]			
1. shock	none	may be present	common
2. blood pressure	no change or rise	falls	falls
3. heart sounds	no change	may be poor	embryocardia, gallop,
4. arrhythmias	none	occasional	common (pericardial) rub
5. heart failure	none	may be present	common
6. fever	absent	frequently absent	present
7. sedimentation rate	normal	frequently normal	abnormal
Electrocardiogram[3]	usually no change or evanescent RS-T depressions	RS-T depressions and T-wave changes for several days or weeks no Q waves or RS-T elevation	RS-T elevation Q waves I and III reciprocal leads progressive pattern, often permanent
Biochemical studies			
serum transaminase[6]	normal		increased 2 to 20 times normal
serum aldolase[7]		normal	increased
plasma isomerase[8]			increased
plasma fibrinogen[9]		normal	elevated
C-reactive protein[9]		negative	positive
serum lactic dehydrogenase activity[4]			increased
Eosinopenia[9]	none		present
Duration of incapacity[3]	minutes to few hours	several hours or weeks	prolonged

Cardiac fluoroscopy, roentkymography and electrokymography give important information in the study of the patient with myocardial infarction.[10] Observation of marked localized diminution or complete or partial reversal of pulsation of the left ventricular border is indicative of a circumscribed area of myocardial damage, usually as a result of previous infarct. Such findings may be observed in the absence of other typical clinical findings of previous myocardial infarction.

Treatment

The occurrence of an acute myocardial infarction often requires prompt decision. Even with incomplete knowledge and in the face of conflicting views the physician must act. An understanding of the sequence of pathological changes that occur and the potential changes in myocardial function are prerequisite for intelligent therapy. In brief,[11] ischemic changes leading to necrosis occur in the muscle within the first few days after the onset of the myocardial infarction. During the second and third week healing processes set in, including fibrosis and the development of collateral circulation. Six weeks are required for most myocardial infarctions to be considered as healed. The severity of the attack depends on the state of the coronary circulation and integrity of the myocardium after infarction. Subsequent possible cardiovascular complications can be prevented or ameliorated by a wise approach in therapy.

Treatment is based on relief of pain and anxiety, rest for the heart during the healing phase, and rehabilitation of patient and family. Symptoms and complications are cared for as they arise.[11] The chief hazard is overtreatment; routine recommendations of standard therapy should be discouraged.[2, 12] Individualization and attention to details are two of the cardinal elements of success.

Relief of pain is the primary objective in therapy.[11, 13] Morphine sulfate 10 to 15 mg. is given at the onset, subcutaneously if the pain is severe, intravenously if the pain is excruciating or unrelieved. Its euphoric action helps allay anxiety. After the initial injection of morphine it is frequently possible to change to meperidine (Demerol) hydrochloride 50 to 100 mg. subcutaneous and later methadone (Dolophine) hydrochloride, given orally in doses of 5 to 15 mg. every three to four hours. Restlessness or continued anxiety can often be partially controlled by phenobarbital 15 mg. four times a day, with larger barbiturate doses at night to insure sleep.

Hospitalization should be considered as soon as the pain has been relieved.[2] If home conditions are satisfactory the majority of patients may remain there, as most attacks run a mild course following the initial pain. A serious condition or unsatisfactory home environment requires removal of the patient to a hospital, immediately, by ambulance.

Oxygen should be administered to patients exhibiting any of the following conditions:[12]

cyanosis
shock
acute pulmonary edema
severe and persistent cardiac pain
congestive failure
certain cardiac arrhythmias
a sharp fall in blood pressure
a rising heart rate
marked leukocytosis
high fever
Cheyne-Stokes respiration not induced by drugs

It is administered as a 50 per cent mixture, 12 to 14 liters per minute, in a cooled tent, for 48 hours to several weeks, depending on need; it may, on occasion, be the crucial factor in saving life.

Relatively few patients with acute myocardial infarction die at the onset

of their illness, indicating that survival of the remainder of these patients depends on what complications resulting from their myocardial damage or temporary impairment of circulatory dynamics may develop.[14] The important complications which can be considered potentially preventable causes of death are shock, serious arrhythmia, thromboembolic phenomena and pulmonary edema.

Shock in some degree is developed in approximately one-half of the patients who survive the onset of an acute myocardial infarction, the mortality rate in this complication varying directly with its severity and duration.[14] Blood transfusions have been disappointing, excessive infusion leading to pulmonary edema or congestive failure or both.[13] The most effective treatment is with vasopressor drugs, the best of which is levarterenol (Levophed) bitartrate.[2, 11, 13] This agent raises the blood pressure to respectable levels and promptly eliminates the symptoms of shock. Undesirable side reactions, as myocardial stimulation, are lacking in levarterenol. The drug is administered by intravenous drip, 4 mg. per liter, in a 5 per cent glucose solution, at the rate of 20 to 30 drops per minute. If the desired blood pressure is not maintained (100 mm. Hg systolic in previously normotensive patients, 120 mm. Hg. systolic in previously hypertensive patients) then the drug concentration is increased; a faster rate of infusion is undesirable because it excessively increases body fluid. When discontinuing the levarterenol a slow drip of 5 per cent glucose solution is substituted to prevent a possible hypotensive recurrence. Levarterenol is intensively irritating if extruded from a vein, causing tissue sloughs; extra precautions should be taken during its administration. Phenylephrine (Neosynephrine) hydrochloride 5 mg. subcutaneously or intravenously every 15 minutes or less, or mephentermine (Wyamine) sulfate 15 mg. intravenously or subcutaneously, or in intravenous drip containing 35 to 70 mg. in 100 cc. of 5 per cent glucose solution, can be used initially until levarterenol can be instituted.

Serious arrhythmias may develop during the course of myocardial infarction in the form of auricular or ventricular premature beats, auricular flutter or fibrillation and auricular or ventricular tachycardias.[11, 12] Unless the patient has a past history of an arrhythmia it is not advisable to administer drugs prophylactically to counteract such irritability. Quinidine is a cardiac depressant with many side affects. This drug should be given only if premature beats are present, its dosage being 0.2-0.4 gm. every six hours. Pronestyl (procainamide) hydrochloride may be substituted for quinidine, 0.25-0.50 gm. administered every six hours. If the arrhythmia is auricular fibrillation or flutter, digitalis is more appropriate as an initial measure. The belief that digitalis in the presence of a myocardial infarct will favor rupture of the myocardium is erroneous.

Paroxysmal ventricular tachycardia presents a special problem in that it cannot be long sustained in patients with myocardial infarction without fatal result; it produces severe cardiac and circulatory stress.[13] Quinidine orally every two hours in increasing dosage of 0.4 gm., 0.6 gm., 0.8 gm. to obtain conversion is given if the general condition of the patient continues to be satisfactory. If the patient's condition is deteriorating, intravenous procainamide hydrochloride diluted in 5 per cent glucose solu-

tion is given at the rate of 50 to 100 mg. per minute until the rhythm reverts to normal or worsens appreciably, the maximum dose being 1 gm. Since intravenous procainamide may cause a considerable lowering of blood pressure, levarterenol may be administered stimultaneously.[2]

Complete heart block with Stokes-Adams syndrome is rare,[13] but if this medical emergency threatens ephedrine sulfate 25 to 50 mg. orally every three to four hours or, if necessary, 1:100,000 epinephrine hydrochloride by slow intravenous injection or epinephrine subcutaneously or intramuscularly may be administered.[11]

Thromboembolic complications in acute myocardial infarction are effectively reduced by anticoagulant therapy.[11, 13, 15] Immediate effects may be obtained with heparin sodium 50 to 75 mg. intravenous or intramuscular every four to six hours, regulating this dosage schedule so that the clotting time is prolonged to not more than twice the normal time at the end of four hours. Blood for the prothrombin test should not be drawn within four hours of heparin administration because of some hypoprothrombinemic effect of this agent. Heparin has the asset that protamine sulfate 50 to 100 mg. intravenous is an excellent and immediately effective antidote, neutralizing the circulating heparin and promptly returning the coagulation mechanism to normal. Simultaneous with heparin administration bishydroxycoumarin (Dicumarol) can be given orally, regulating the maintenance dose so that the prothrombin is 20 to 30 per cent of normal. When this is achieved, usually within 48 to 72 hours, heparin can be omitted. Anticoagulant therapy should be continued until the patient is ambulatory. Anticoagulants should be employed in most patients with acute myocardial infarction, noting the following contraindications to or indications for caution:[15]

- gastrointestinal bleeding
- peptic ulcer
- recent fracture or bone fusion operation
- recent prostatectomy
- recent central nervous system operation
- increased capillary fragility
- thrombocytopenia
- renal insufficiency
- severe hypertension
- possible cerebral hemorrhage
- pregnancy
- subacute bacterial endocarditis
- liver disease (cirrhosis or hepatitis)
- congestive heart failure
- depletion of vitamin K stores or prothrombin reserves—
  - cachexia
  - oral antibiotic therapy
  - parenteral feeding
  - malnutrition
- history of bleeding with previous anticoagulant therapy
- inadequate or undependable laboratory facilties for prothrombin determination
- immediate postpartum or postoperative period
- nonspecific pericarditis[2]
- ulcerative colitis[2]

Pulmonary edema is a common occurrence in patients with myocardial infarction. It is treated as if myocardial infarction were not present.[2, 13] The patient is elevated to a sitting position in bed. Morphine sulfate 30 mg. hypodermically or intravenous is usually efficacious but intravenous aminophyllin and strophanthin may be necessary. Aminophyllin 0.5 gm. is admin-

istered slowly. The initial dose of strophanthin K is 0.25 mg.; 0.1 mg. injections may be repeated every hour until 1 mg. has been given in 24 hours. Oxygen under positive pressure, tourniquets on all four extremities, leaving one cuff loose and rotating every 15 minutes, phlebotomy if shock is not present, and an intravenous mercurial diuretic may be helpful. Occasionally the inhalation of alcohol vapor 20 to 30 per cent to reduce foaming in pulmonary edema has been effective. These patients should receive anticoagulant therapy even if the sputum is bloody.

Minor disturbances are often quite upsetting to the patient and may even lead to serious consequences. Nausea and vomiting may be prevented by abstinence from fruit juices, cold milk, spicy foods and treated with dimenhydrinate (Dramamine) 50 mg., chlorpromazine (Thorazine) 10 to 25 mg., or cyclizine hydrochloride (Marezine) 25 to 50 mg. orally, intramuscularly or by suppository.[2] Hiccough will almost always subside with constant reassurance. If not, remedial procedures as chlorpromazine, ethyl chloride spray along the diaphragm, and atropine sulfate intravenous have often proved successful.

During the period of bed rest the patient need not be so restricted as to caution against wiggling the fingers, moving the arms, or turning on the side with help.[12] The upper segment of a hospital bed can be raised so that complete recumbency with the attendant slight increase in the work of the heart is avoided. The patient should feed himself as soon as he is able. Constipation may be present because of the effect of morphine, lack of activity, and limited food intake. Mineral oil or milk of magnesia at night, assisted by a small saline enema in the morning, may initiate movements after the early period has passed and prevent straining at the stool.[13] Use of the bedpan often requires much physical effort and mental stress. Careful lifting of the patient onto a bedside commode or nearby bathroom commode is saving in cardiac effort and is usually considerably more acceptable. Gentle foot and leg exercises are advisable to prevent stasis of blood in extremities. Patients suffering mild attacks of myocardial infarction are kept in bed approximately one week unless it is felt that sitting up in a chair earlier than this period is necessary to raise morale.[2]

In more severe attacks the patient remains in bed for longer periods of time.[13] During the third and fourth weeks increased movement of the extremities in bed is allowed. While sitting, the patient may engage in occupational therapy within his capability, read newspapers and magazines that he can manage by himself. Letter-writing may be permitted, as well as an increasing number of short visits with friends. During the fifth and sixth weeks standing leads progressively to walking on the level and the beginning of stair-climbing.

The electrocardiogram is not depended upon as a criterion for determining the progress of the patient or for deciding when he may sit up, begin to walk or return to work.[2] If the clinical course is satisfactory the patient may get up and walk even though the electrocardiogram shows marked alterations. Nor is too much reliance placed upon the sedimentation rate as a guiding factor in treatment.

A planned dietary regimen seems worthwhile in these patients.[2, 12] Lowering fat intake may retard or even reverse arteriosclerotic processes,

decreasing the likelihood of future complications. Dieting decreases the work of the heart and prevents gastro-cardiac reflexes. During the first few days or weeks 700 to 1200 calories suffice; thereafter the intake may be gradually increased. Fried foods, the fatty parts of meat, cream, creamed soups, and thick gravy are omitted. Butter may be used in moderation, lean meats, eggs, and ordinary cheese are allowed in limited amounts. Consumption of skimmed milk, cottage cheese, green and yellow vegetables is encouraged. A moderate dieting regimen of this nature can be followed without great hardship or difficulty.

Regarding tobacco there is no proof that it aggravates coronary atherosclerosis while it appeals to people all over the world. The physician should carefully evaluate the importance of this restriction in a person who is already limited in so many ways. The same applies to the moderate use of alcohol.[11]

The vast majority of patients surviving myocardial infarctions make a fair or good recovery; over half of the patients make an excellent functional recovery.[2] Four out of every five patients are able to resume work following coronary occlusion and can lead productive lives for many years. Very mild cases may be ready to return to work within two to three months, more severe cases within three to six months.

Addendum: At Jefferson Medical College Hospital, the prothrombin level is kept at 10 to 20 per cent.

SUMMARY

In patients suffering an attack of myocardial infarction the history and symptoms are often sufficient to make a tentative diagnosis. Serial changes in the electrocardiogram are valuable but not essential. The diagnosis must be established by evidence of muscle necrosis.

The chief hazard in treatment is excessive therapy. Individualization and attention to details are two of the cardinal elements for success. Symptoms and complications should, in general, be treated as they arise. The chief complications which are potentially preventable causes of death are shock, serious arrhythmia, thromboembolic phenomena, and pulmonary edema.

A vast majority of these patients make a fair to good recovery and can lead productive lives for many years.

RESUMEN

En los enfermos que sufren un ataque de infarto del miocardio, los síntomas y la historia clínica a menudo bastan para hacer un diagnóstico preliminar. Los cambios en la serie de electrocardiogramas son valiosos pero no esenciales. El diagnóstico debe establecerse por la evidencia de la necrosis muscular.

El principal riesgo en la terapéutica es el tratamiento excesivo.

Son elementos cardinales para el buen resultado la individualización y la atención a los detalles. En general, los síntomas y las complicationes deben tratarse conforme se presenten. Las principales complicaciones que son posibles de prevenirse como causas de muerte son el shock, la arritmia grave, fenómenos tromboembólicos, y el edema pulmonar.

Una amplia mayoría de estos enfermos se recuperan bastante bien o bien y pueden llevar una vida productiva por muchos años.

RESUME

Chez des malades atteints d'infarctus du myocarde, l'histoire et les symptômes sont souvent suffisants pour permettre une tentative de diagnostic. Des al térations répétées sur l'électrocardiogramme sont valables mais pas essentielles. Le diagnostic doit être établi par la preuve d'une nécrose musculaire.

Le principal danger du traitement est réalisé par une thérapeutique excessive. L'individualisation et l'attention donnée aux détails sont deux des principaux éléments de succès. Les symptômes et les complications devraient, en général, être traités dès qu'ils apparaissent. Les principales complications qui sont des causes cependant évitables de la mort sont le shock, l'arythmie grave, les phénomènes thrombo-emboliques, et l'oedème pulmonaire.

Une grande majorité de ces malades obtinrent une guérison convenable ou bonne, et purent mener une vie active pendant plusieurs années.

ZUSAMMENFASSUNG

Bei Patienten die an einem Anfall von Herzinfarkt leiden, reichen oft Vorgeschichte und Symptome aus, um eine vorläufige Diagnose zu stellen. Serienveränderungen im Elektrocardiogram sind von Wert, aber nicht wesentlich. Die Diagnose muss begründet werden durch Anzeichen von Muskelnekrose.

Das Hauptwagnis bei der Behandlung ist die intensive Therapie. Anpassung an den Einzelfall und Beobachtung von Einzelheiten sind zwei der cardinalen Elemente für einen Erfolg. Symptome und Komplikationen müssen im Allgemeinen behandelt werden, sobald die auftreten. Die Hauptkomplikation, die potentiell vermeidbare Todesursachen sind, sind Schock, schwere Arrhytmie, embolische Erscheinungen und Lungenödem. Eine erhebliche Anzahl dieser Patienten erholt sich leidlich und gut kann viele Jahre lang ein produktives Leben führen.

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The Diagnosis and Treatment of Acute Coronary Heart Disease Without Objective Findings

There are patients with acute coronary heart disease who have no objective evidence of myocardial infarction by electrocardiogram or laboratory tests, in fact who have no objective evidence of any cardiac change whatsoever. In such patients, the clinician, purely on a history as he obtains it, is faced with the necessity of making a diagnosis which carries with it at least initially, potential consequences of grave significance. The complexity of such a serious diagnosis is compounded by the fact that the history is usually atypical. It is such atypical histories that frequently lead to a reassuring pat on the back with some vague remark about "muscle pain." It is also such histories that occasionally end with sudden death.

Given a patient, middle aged or beyond, with a vague chest discomfort that has no diagnostically helpful relationship, and in whom there are no objective evidences of heart disease, one is faced in the first instance with the necessity of excluding acute coronary heart disease. In the usual situation any other diagnostic possibility is such that it can await the fullest possible consideration of the cardiac status. If an electrocardiogram can be recorded during the course of the pain, transient ischemic changes will occasionally be diagnostically helpful. If such changes are not observed, it is my belief that any suspicion of an acute coronary episode should justify a tentative diagnosis of acute coronary heart disease. The index of suspicion should be especially high in any patient middle aged or above who *spontaneously* develops chest or upper abdominal distress of any sort that is not clearly or easily identifiable as due to some non-cardiac cause. In such a situation one can do little more than conclude that it is impossible to eliminate acute coronary heart disease as a diagnosis. Therefore, it is impossible to exclude the possibility of sudden death, or of the development of a major myocardial infarction. Since such serious complications cannot be discounted, management must be directed accordingly. Even a known history of peptic ulcer or x-ray evidence of gallstones should be ignored initially unless the clinical picture can be surely related to these conditions.

There should be no diagnostic difficulty when a patient presents himself with a history that is fairly typical of the pain of acute coronary heart disease but without objective findings. This includes patients with the onset of classical angina of effort, or the acute worsening of pre-existing angina. The typical history should suffice for a tentative diagnosis of acute coronary heart disease. The patient with an atypical history, however, may present himself with little more than mild to moderate substernal discomfort that comes and goes spontaneously and is often associated with belching and indefinite upper abdominal distress, in other words "indigestion." The discomfort may extend into the neck. If the

distress comes on when the patient is in the supine position, relief may be noted in the sitting position. There may be a feeling of restlessness and even of concern without good reason for such concern.

A patient with chronic fatigue, "sticking pains" in the chest, precordial aches, tenderness of the chest wall, deep sighing respirations and other evidences of cardiac neurosis needs especially to be recognized and not confused with the patient with atypical acute coronary heart disease for obvious reasons. This is not the place to review the differential diagnosis. I might repeat, however, that the sudden otherwise unexplained onset of the atypical history in a patient in the "coronary" age should in itself provide a background for a proper evaluation of the diagnosis of acute coronary heart disease.

There are several factors that make the approach to therapy difficult. In the first place, there is the impossibility of establishing a positive diagnosis. In the second place, there is the clinical experience that most patients with this form of acute coronary heart disease do not die suddenly or develop a major myocardial infarction; that is to say, most such patients recover spontaneously. (Hence it is unfortunate that this state is often referred to as "impending myocardial infarction." One might perhaps more properly refer to it as "impending recovery," since most do recover. I prefer the term "smoldering coronary heart disease" for this phase.) Finally, there is the disturbing fact that even when the diagnosis is definite, the benefits of therapy are at best uncertain and the approach more or less empiric. In fact, there is some question as to what, if anything, is accomplished by therapy.

Treatment must be viewed in terms of what one hopes to accomplish. In the problem under discussion these hopes are directed toward (a) the prevention of sudden death, and (b) the prevention of a major myocardial infarction. In regard to both of these complications, the basic therapeutic considerations concern themselves with rest and anticoagulants.

Two questions must be answered in regard to rest. How complete should the rest be, and how long should it be continued? As to the first question, if rest is useful at all, then maximum rest should be most useful. Rest is recommended on the assumption that the heart is laboring under difficulties following an acute change in the coronary circulation presumably with ischemia. An increase in ischemia from an overactive heart might result in a sizeable infarction or it might conceivably increase the likelihood of ventricular fibrillation with sudden death. Under the circumstances, it would seem reasonable to recommend complete bed rest modified perhaps with the use of a bedside chair, restriction of visitors, and sedation; a program much as one would recommend for a patient with recognized myocardial infarction. Therapy is indeed based on the assumption that there may be a minor myocardial infarction.

The duration of treatment presents a difficult problem. In the presence of a major myocardial infarction the period of rest is largely determined by the knowledge of the time required for the complete healing of an infarction as well as the empiric observation that serious complications rarely occur after about four weeks. In the case of smoldering coronary heart disease, and especially when the diagnosis is not firmly established,

there are several important considerations. (a) Is it economically, practically and psychologically feasible to put a patient to bed for a long period of time on the basis of a necessarily uncertain diagnosis? (b) Assuming the diagnosis to be correct, at what point can the acute phase be said to have passed into the chronic or stabilized phase with a coronary status that is usually not far removed from the normal?

In answer to the first question, it may be said that the possibility of serious complications makes it not only reasonable but necessary to treat a patient intensively. The patient can and should be told that there is some doubt about the diagnosis and that he is being put to bed as a precautionary measure. But he should also be told that after a few weeks it can reasonably be anticipated that he can carry on more or less normally. The undue concern over the presumed acute phase can be balanced by the strong reassurance regarding the subsequent course. Under these circumstances, a suitable period of rest will generally be found to be readily acceptable. It is of course not clear as to just what a "suitable period" is, but two weeks of bed rest followed by two weeks of restricted activity within the home would seem to be justifiable on the basis of the observation that the period of one month will in almost all instances cover the period of possible complications.

Currently there is not enough evidence to answer with finality the question as to whether anticoagulants are helpful. The theoretical justification for such therapy in the patient with smoldering coronary heart disease is that the anticoagulants might prevent the development of a larger thrombus and hence a major myocardial infarction; this on the assumption that the smoldering state is brought about by a small thrombus producing either vascular narrowing or occlusion. Anticoagulants would of course also be helpful in preventing phlebothrombosis during the period of bed rest. There are sufficient data to suggest that anticoagulants are effective in the situation under discussion. Hence, where anticoagulants can conveniently be given they should be given. Thus if the patient is in the hospital and therapy can be relatively easily controlled, there is probably more to gain than to lose by giving anticoagulants.

It has lately become evident that a patient who makes a good recovery from an acute coronary attack and has no recurrence for a year or so has a life expectancy not very different from that of an apparently normal person. It is also known that most patients beyond middle age who are presumed to be normal do in fact have demonstrable evidence (at death from non-cardiac causes) of significant coronary artery disease in the form of one or more coronary occlusions. We have come to realize, therefore, that patients with chronic stabilized and clinically recognizable coronary heart disease, i.e., those who have made a good recovery from an acute attack, are not as sick as we once thought they were; while on the other hand, people beyond middle age who are thought not to have heart disease are not as well as we once thought they were. The two groups have come remarkably close together. This concept has had a great influence on the management of patients with chronic coronary heart disease as well as so-called normal people.

A by effect of this concept is that if a patient can be brought through

an acute episode without damage, his outlook is indeed good; hence the special justification for extreme caution in the diagnosis of the acute episode and for extreme care in its management. Given a patient with *chronic* but equivocal evidence of cardiac pain a non-cardiac diagnosis is preferable on the assumption that if the pain is per chance cardiac in origin no damage is done if the diagnosis is not made, whereas considerable psychological damage might be done by a wrong diagnosis of cardiac distress. On the other hand, given a patient with *acute* but equivocal evidence of cardiac pain a cardiac diagnosis needs to be made because in such a case an error in not diagnosing cardiac distress may produce much more serious consequences than an error in falsely diagnosing unimportant non-cardiac discomfort. In other words, in chronic coronary heart disease it is safer to "underdiagnose," in acute coronary heart disease it is safer to err in the opposite direction.

A recognition of these developing concepts will in and of itself do much to determine the approach to the diagnosis and hence the management of acute coronary heart disease when it presents itself with an atypical story and with no objective findings.

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ELECTROCARDIOGRAM OF THE MONTH

Vagal Hyperirritability

Mrs. R. G., a 61-year-old white female, was admitted to the Clinic Hospital on November 21, 1957. Her admitting complaints suggested angina pectoris which was strengthened by a history of hypertension (initial blood pressure was 240/120 which dropped during hospitalization to 162/80) and a presumed episode of coronary insufficiency two years previously. During her hospital stay she also had symptoms suggestive of a duodenal ulcer which had been diagnosed by x-ray in 1954 and which was still present in her most recent x-rays. Her response to ulcer treatment was inconclusive. Roentgenographic examination of her gall bladder and heart were normal.

From the clinical standpoint, this patient's symptoms could be due either to angina pectoris or an active duodenal ulcer, or both. The resident staff were inclined to the former diagnosis, because of the inverted T waves in Leads V2-V3 (see control tracing). In view of the ulcer history, and since the author had previously noted that vagal stimulating drugs can cause such T wave inversions, intravenous atropine 0.86 mgs. was given by rapid injection. The T waves in Leads V2-V3 became upright about one minute after the intravenous atropine injection and remained so for about three minutes. A similar study done the day previously utilizing the same volume of normal saline injected into the same vein had no effect on the electrocardiogram.

Such results do not usually occur when the precordial T wave inversions are the result of organic heart disease. We believe that the post-atropine findings strongly suggest vagal hyperirritability and that the latter is characterized by shallow inversion of precordial T waves most commonly in the right precordial leads. This does not mean, however, that this patient may not have organic coronary disease although this was not documented during or after the period of hospitalization. Four months after discharge, her electrocardiogram was unchanged (see control tracing).

Past history of upper gastrointestinal disease with T wave inversions, chiefly in the right precordial leads, should arouse the suspicion of vagal hyperirritability which can be demonstrated by the intravenous injection of atropine.

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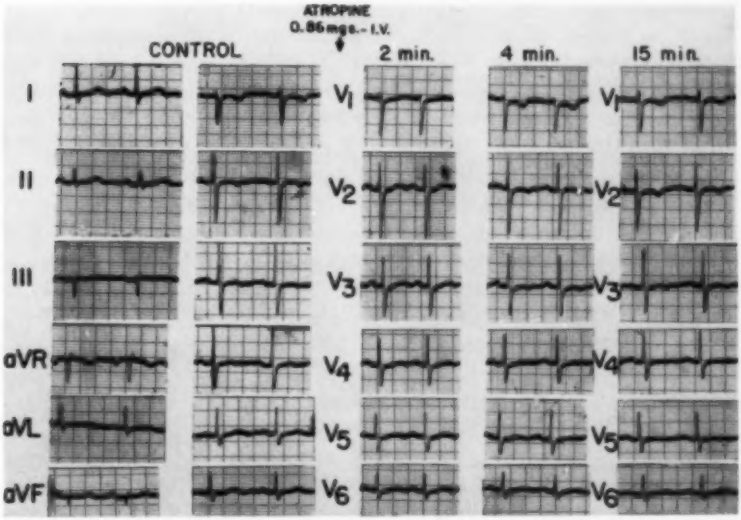

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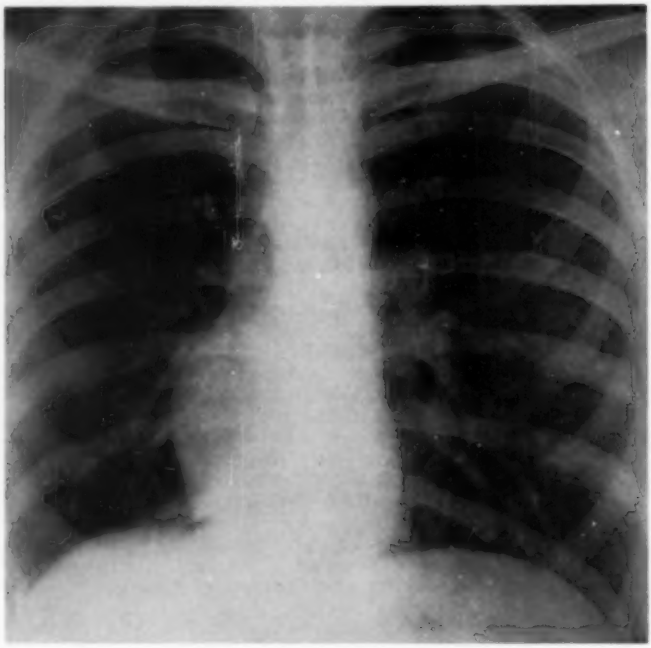
X-RAY FILM OF THE MONTH

Clinical Information

An asymptomatic white woman. Physical examination normal. No cardiac murmurs. Electrocardiogram normal.



ANSWER—*Dextroversion of the Heart*

This is a congenital variation in which the heart is rotated into the right thorax. The cardiac chambers retain their normal relationship to each other and the aortic knob and descending aorta lie in normal position. In some cases a film made with the patient rotated about 10 degrees into the right anterior oblique position will give the appearance of a normal heart as ordinarily seen in the true anteroposterior projection.

Differentiation from total situs inversus is easily made from the normal position of the aortic knob and the abdominal viscera. Isolated dextrocardia, in which the chambers are reversed, is nearly always associated with severe symptomatic cardiac anomalies and an abnormal electrocardiogram. In dextroposition of the heart resulting from pulmonary collapse or emphysema or from deformities of the thoracic cage the abnormality causing the right-sided cardiac shadow is generally obvious. As a general rule, dextroversion represents an incidental but confusing finding.

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Obstructive Segmental Emphysema After Chest Trauma

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Since 1939, when the concept of infantile lobar emphysema was introduced, approximately 40 recognized cases have been reported in the medical literature. Several etiologies have been proposed[2] and in general these have been grouped into lesions of the bronchi or of the pulmonary parenchyma. The following case report appears to be of some significance in that it introduces external trauma as an additional possible etiology.

Case Report

A three month old white girl was involved in an accident in which she was lying on the rear seat of an automobile when it struck a telephone pole causing the infant to be thrown forcibly into the back-rest of the front seat. She was admitted to St. Luke's Hospital immediately on August 24, 1956 when she appeared to be in acute respiratory distress. There was stridor, indrawing of the intercostal spaces, especially noted on the right. Respiratory rate was markedly increased (40/min.), pulse rapid (130), and there was circumoral pallor. She was placed in an oxygen tent and x-ray films of the chest were taken. The following day when seen by one of the authors, in addition to the stated findings, there was notable cyanosis. The presence of shifted mediastinum and the absence of peripheral lung markings with atelectasis of the lower lobe suggested the diagnosis of tension pneumothorax of the right chest. A chest catheter was introduced into the pleural space and attached to under-water seal drainage. There was immediate improvement in her condition. During the next two weeks her pulmonary status seemed to stabilize and she was discharged to the care of her pediatrician. A careful history and examination of the natal records showed no evidence of previous pulmonary disease. Her physician considered the child completely normal prior to the described injury.

On January 23, 1957 she was readmitted to the hospital with the signs of acute lower respiratory infection. She seemed extremely ill. The syndrome of stridor, indrawing of the right intercostal spaces and cyanosis was again apparent. Her rectal temperature was 104° and pulse 140. Examination of the chest showed hyper-resonance on the right side with absent breath sounds. The right side of the chest appeared to be fixed in the inspiratory position. X-ray film showed increased air content on the right, peripheral lung markings were absent, and marked mediastinal shift to the left with an apparent herniation of right lung through the anterior mediastinum.

A tentative diagnosis of traumatic lung cyst was entertained. She was treated supportively and with antibiotics. Again there was a regression of symptoms and with pulmonary stabilization but with persisting insufficiency. A decision was made to explore but because of repeated severe episodes of lower respiratory infections, surgery was postponed.

On October 22, 1957 right thoracotomy was performed.

Operative note: Inspection of the right lung revealed tremendous emphysematous hypertrophy of the middle lobe, which on close examination proved to be the lateral segment of this lobe. The emphysematous segment filled the right chest cavity, compressing the remaining lung, and herniating through the anterior mediastinum toward the left chest. The hilar dissection proved to be relatively easy and the resection of the involved segment was accomplished without incident. Inspection of the transected bronchus showed it to be stenosed. On completion of the bronchial closure, the residual lung was aerated without difficulty. Two number 18 rubber chest catheters were placed in the pleural space and attached to an under-water drainage system. She withstood the procedure well.

The subsequent hospital stay was completely uneventful and she was discharged from the hospital on the 12th postoperative day.

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Pathological Report: Gross: Flat portion of lung 13 x 8 x 1 cm. Surface everywhere covered by an intact pleura which is a dark pink over two-thirds of the surface, and white over the remaining one-third with no sharp color demarcation. Seen from above the tissue is somewhat kidney shaped. The point of attachment and the entrance of vessels and air tubes are eccentrically placed in fleshier red portion. Section gives rise to an outpouring of cherry-red frothy fluid. Dissection discloses no air tubes of any size; none larger than 1 or 2 mm. Microscopic: Many of the alveoli contain blood or sanguineous fluid. The greater part of this may be operative trauma. Many of these alveoli are over-expanded and ruptured, not an artefact, but true marked emphysema.

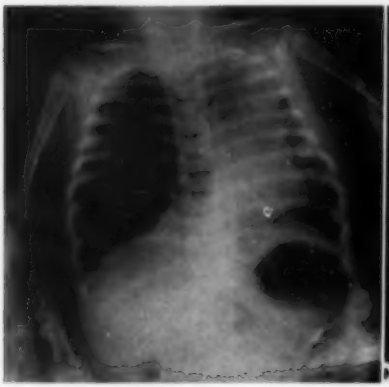

FIGURE 1

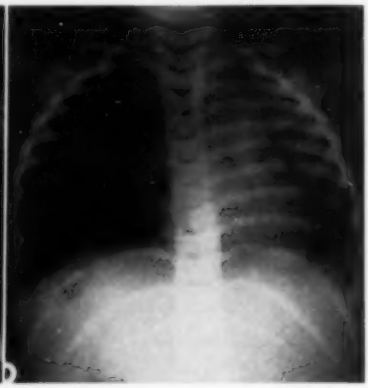

FIGURE 2

Figure 1: PA roentgenogram on original admission which suggested the diagnosis of right pneumothorax.—*Figure 2:* Immediately preoperative PA roentgenogram showing increased aeration of right chest with shifted mediastinum and mediastinal herniation of right lung.

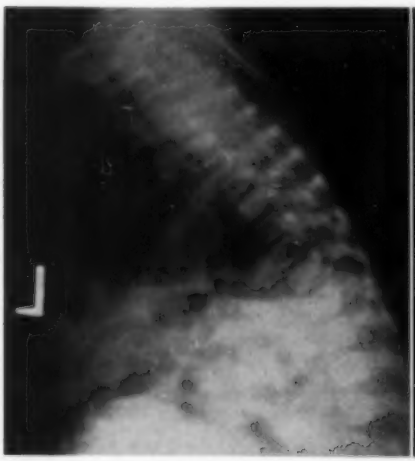

FIGURE 3

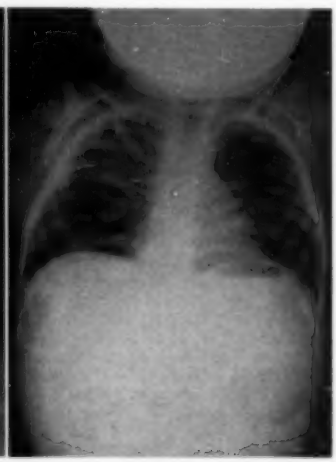

FIGURE 4

Figure 3: Lateral view of immediately preoperative roentgenogram which demonstrates particularly well the mediastinal herniation of right lung.—*Figure 4:* Postoperative PA roentgenogram showing return of mediastinum to midline and normal markings of right lung.

Verhoff-Van Gieson stains for elastic tissue show none in the alveolar walls or in the peribronchial tissue. The contral ends of the larger bronchioles seen in the section show foci of cartilage matrix, but not actual cartilage, and these occur as isolated beads. Bronchioles seem unduly expanded, suggesting bronchiectasis; but there is no zoning with any inflammatory cells.

Discussion:

Infantile lobar emphysema is an established entity. Although it is a rare condition, recent interest has led to more frequent recognition of this disease. It occurs in the newborn, usually during the first few months of life. These infants present the picture of an acute respiratory emergency. Frequently, there is a history of recurrent attacks of dyspnea and cyanosis dating back to the immediate neonatal period. In some of the infants there is a definite history of difficult resuscitation following delivery. The findings are that of expiratory dyspnea, cyanosis, retraction of intercostal spaces and indrawing of the supra-sternal area. Physical examination suggests emphysema of one lung and x-ray film shows herniation to the contra-lateral side with shifting mediastinum. There is also an associated atelectasis of the uninvolved lobes. The x-ray film diagnosis is often difficult and frequently confused with pneumothorax or congenital cystic disease.

Pathology: The typical pathological picture of this condition is a markedly distended segment or lobe of the involved lung with associated atelectasis of some of the other parts of the lung. Most commonly involved are the upper lobes. Microscopically, there is frequent evidence of bronchiolar hypolasia, alveolar over-distention and rupture. Boland, et al.[2] have described the frequent deposition of collagenous connective tissue in the alveolar supportive stroma.

Etiology: Several theories as to the etiology of this entity have been advanced. These appear to fall into three major categories: bronchial lesions, extrinsic bronchiolar compression, and lesions of pulmonary parenchyma.

I. Bronchial Lesions:

In 1939 Overstreet[1] in the first published account of this condition described a deficiency of the cartilage rings in the left upper lobe bronchus. Subsequently others have reported similar findings.[3, 4] Robertson and James reported two cases of obstructive emphysema due to hypertrophied mucosal folds.[5]

II. Extrinsic Bronchial Compression

Fischer, Potts, and Hollinger have reported this disease due to bronchial compression from anomalous vessels.[6]

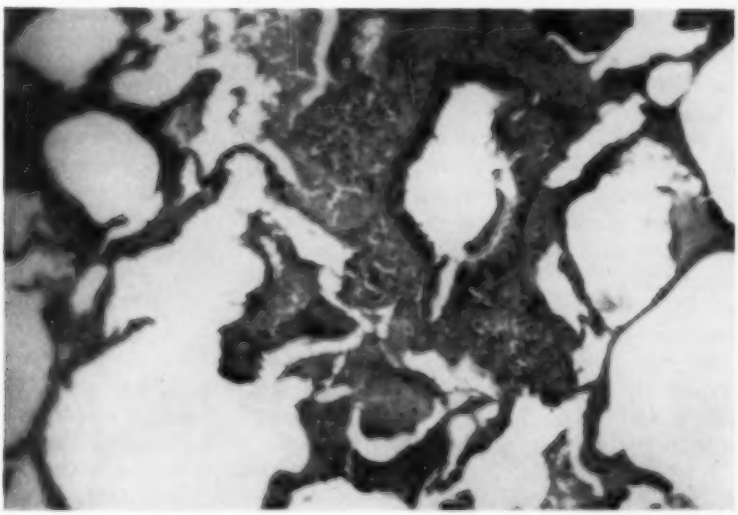

FIGURE 5: Photomicrograph showing a typical area of the involved segment as described in pathology report.

III. Lesions of Pulmonary Parenchyma

Early concepts held that there was diminution of elastic tissue in alveolar walls in this disease.[7] This theory is no longer tenable since elastic tissue is meager in normal infants.

Overly vigorous attempts at resuscitation[8] of the apneic newborn may be a contributive factor in the production of this condition (intrinsic trauma).

IV. Extrinsic Trauma as Suggested by This Case

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Aneurysm of the Pulmonary Artery

Report of a Case Diagnosed by Angiocardiography and Explored Surgically

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Aneurysmal formations in the pulmonary artery fall naturally into two well defined groups, each with its different causes and incidences. Lesions of the peripheral branches are relatively common. They are produced either in a mycotic manner from within by infected emboli or perhaps more frequently by erosion from without by an infective process as is the case with the so-called Rasmussen aneurysms in the walls of tuberculous cavities.

In complete contrast, the incidence of aneurysmal dilatation of the main pulmonary artery or of one of its major subdivisions is of considerable rarity. Blades, Ford and Clark (1950) found a total of 152 adequately documented cases in the world literature up to that time. Of these, no less than 147 have been exhaustively studied in two major surveys. Boyd and McGavack (1939) reviewed 111 cases while Deterling and Clagett (1947) contributed a further 36. The condition was described in another five patients in the ensuing three years. The rarity of the condition is underlined further by the fact that not a single instance of it was unearthed in the course of 37,757 consecutive autopsies undertaken by Jennes (1936). Deterling et al quoting a report by Blakemore of the Presbyterian Hos-

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pital, New York, recorded that in a series of 456 intrathoracic aneurysms there was none involving the pulmonary artery.

Of the 147 cases comprising the two principal reviews, about 30 per cent were attributed to syphilis. With the general decline in venereal infections, doubt has been cast on this figure by later authors. Congenital cardiac defects, with persistent ductus arteriosus and inter-atrial septal defect the main offenders, were the next commonest source. Mycotic and traumatic causes were dubious and rare.

The age and sex incidences are of interest when compared with aneurysms of syphilitic derivation. There was equal sex incidence in the 36 pulmonary aneurysms described by Deterling et al. Syphilitic involvement of the aorta on the other hand is a predominantly masculine affliction (Lewis, 1943). In addition, the pulmonary artery dilates at an earlier age than the aorta weakened by specific disease. Deterling found the average masculine age to be 42 years and the feminine age 39 years.

The site of dilatation is of supreme importance now, when ligation of an aneurysmal branch offers hope of cure. A case treated in this way has been reported. (Blades et al, 1950). Boyd et al (1939) reported a main trunk incidence of 66 per cent, the aneurysm involving one or other branch either alone or in conjunction with the main artery. The aneurysm was usually of a saccular type, fusiform dilatation being less common.

The following case is of interest in that accurate diagnosis was established pre-operatively by angiocardiography. The diagnostic value of contrast angiography was stressed by Priviteri and Gay (1950). Despite the predominance of main stem dilatations is was considered justifiable in our

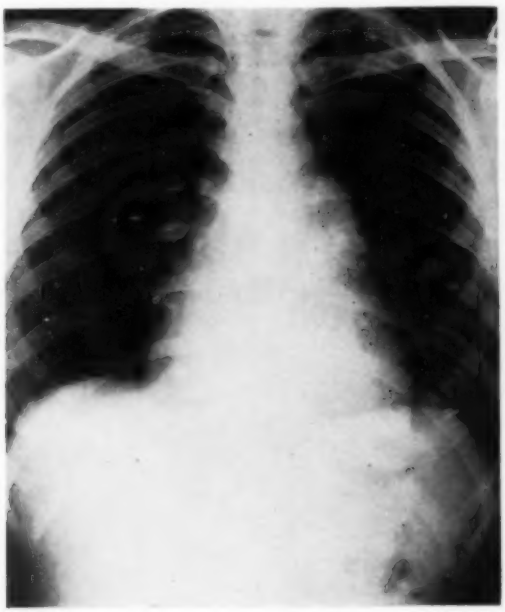

FIGURE 1

patient to proceed with surgical exploration to assess the possibilities of branch ligation.

Case History: The patient, a woman of 27 years, was admitted to the Thoracic Unit, Mearnskirk Hospital on March 19, 1954 for cardiac investigation. She had been apparently in perfectly normal health until three years previously when she developed a left sided pneumonic illness for which she received penicillin at home. Her recovery was satisfactory, but she was told that she had a cardiac murmur. Two years later she became pregnant, and in the last trimester developed progressive exertional dyspnoea. A full-term normal child was born six months before admission, and after this she appeared to regain most of her exercise tolerance. There was still, however, minor residual breathlessness on such exertion as going upstairs. She could walk any distance on the flat, and could perform all her housework. There was no chest pain, palpitations, oedema, or upset of renal, bowel, or menstrual functions. She had had one previous uneventful pregnancy, and there was no other relevant antecedent illness.

Her general condition was good, and there was no evidence of dyspnoea, cyanosis, finger-clubbing, or oedema. The blood pressure was 110/70 mm. of mercury, and the heart was in sinus rhythm. A loud, blowing systolic murmur, with coarse accompanying thrill, was found in the third left interspace close to the sternal border. There was some conduction of the bruit down the sternum into the fourth and fifth interspaces. A faint diastolic component was also audible at the pulmonary area. The heart sounds were closed at the other areas, and there was no abnormality of the respiratory system.

Radiological examination revealed considerable dilatation of the pulmonary conus but no undue vascularity of the lung fields (Fig. 1). Ba. swallow and fluoroscopy showed some enlargement of the right ventricle, marked pulsation of the pulmonary conus, and hilar dance. Electrocardiography demonstrated inversion of T. waves in leads V1 and V2, with some increase in the height of R. in those same two leads. Those changes were interpreted as indicating a mild grade of right ventricular hypertrophy.

Phonocardiography showed that the murmur was loudest in early systole, but became fainter during the second half of the systolic phase. It reappeared at the beginning of diastole, and virtually disappeared in the second half of diastole (Fig. 2). Cardiac catheterization was performed, and demonstrated merely a mild rise in pulmonary artery pressure when the catheter tip was in the pulmonary conus dilatation (22.5 mm. of mercury). The percentage oxygen saturation figures were within the normal ranges. The erythrocyte sedimentation rate was normal, and the Wassermann reaction was negative.

At this stage a preliminary diagnosis of pulmonary artery aneurysm was made, and angiocardiography under basal sedation was performed on March 24, 1954. Fig. 3 shows the large dye-filled aneurysmal sac. Although the appearances suggested main artery dilatation, surgical exploration was considered advisable, for final assessment.

Left thoracotomy was performed on April 2, 1954. The extrapericardial pulmonary circulation was found to be normal, but incision of the pericardium revealed a large fusiform dilatation of the whole length of the main pulmonary artery. The ligamentum arteriosum was exposed but was not patent, and no other intravascular communications were found. As surgical correction was impossible, the chest was closed.

The post-operative course was devoid of incident, and she was discharged in May, 1954. She returned for out-patient examination on August 12, 1954, and on her own

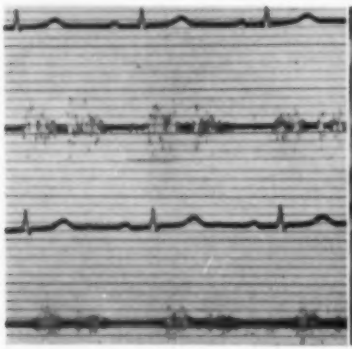

FIGURE 2

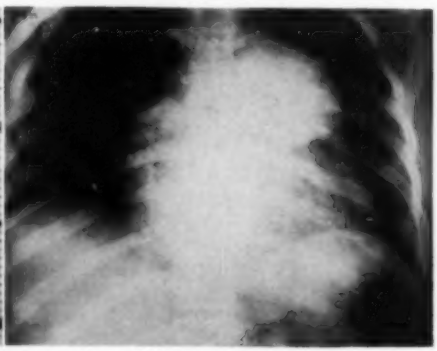

FIGURE 3

testimony felt well. Her husband reported, however, that her breathlessness was becoming increasingly prominent. Clinical examination confirmed this deterioration, and a chest skiagram showed quite definite enlargement of the aneurysm. Later attempts to contact her through the medium of her husband failed to elicit a reply, but we feel she must now assuredly be dead.

Discussion

Although very rare, aneurysms of the main pulmonary artery or of one of its major branches carry an extremely poor prognosis. A fatal outcome is accomplished either by right heart failure or by rupture of the aneurysm into the pericardium, pleural sac, or even the bronchial tree. Although Wood (1950) stated that rupture was rare, Deterling et al mentioned it as a common cause of death. Wilkinson (1950) described fatal rupture in a young girl and Blades et al stated that about one third of all such aneurysms end in this manner. If at all possible, therefore, surgical intervention should be considered provided preliminary investigations indicate any possibility of success. In this investigational connection angiocardiography must play an important part.

The aneurysm in our case would appear to be due to a congenital defect in the wall of the main pulmonary artery. Unfortunately there is no histological proof to support this, but pre-operative investigation ruled out specific infection, congenital cardiac defects, the producers of cor pulmonale, mitral stenosis, idiopathic pulmonary hypertension, etc.

Acknowledgments: We wish to accord our thanks and appreciation to Mr. R. S. Barclay, Thoracic Surgeon, Mearnskirk Hospital, in whose wards the patient was investigated, and who operated on the patient. The authors are indebted to Dr. A. A. F. Peel, Victoria Infirmary, Glasgow, for the cardiac catheterisation and phonocardiography findings.

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Editorial

Long-Term Results of Chemotherapy in Tuberculosis*

Do long-term results of chemotherapy refer to long-term results of long-term chemotherapy, long-term results of short-term chemotherapy, long-term results of chemotherapy with surgery, long-term results of chemotherapy alone, or long-term results of chemotherapy in preparation for surgery? And on what types of cases do you do surgery? And how long is long-term? The title-question is complex.

Unquestionably, chemotherapy keeps patients alive longer. The results in this regard have been spectacular. But proof of *cure* of tuberculosis requires life-long interest and observation. Although most relapses prior to the era of chemotherapy occurred within five years, some appeared much later. De Friez, et al.,[1] reporting on a long-term follow-up of patients treated without chemotherapy in the 1930's, found a cumulative relapse rate at five years of 32 per cent—and a rate of over 50 per cent at 20 years.

This state of affairs may still obtain. There are indications that the figures on late relapse after short-term chemotherapy may not be very much better than were our long-term results after rest or collapse therapy. Some of the answers are beginning to emerge from the large-scale beautifully controlled Army-Navy-Veterans Administration studies. For example—Falk,[2] reporting on bone tuberculosis to the 16th Veterans Administration Conference, this year, found a cumulative rate of relapse and new tuberculous lesions of 35 per cent at five years after termination of chemotherapy. Lattimer,[3] at the same meeting, gave these figures for advanced renal tuberculosis: Three years after chemotherapy about 90 per cent had negative urine cultures; five years after treatment only 75 per cent were negative; six years after treatment only 50 per cent were negative. In the case of tuberculosis of the lung, practically everyone now agrees that if, after 6-12 months of chemotherapy, cavity is still patent, there is little chance of cavity-closure by chemotherapy alone. But what is happening after resection of the cavity when the chemotherapy is stopped? Raleigh[4] found that in 78 resected "open negative" cases, 15 per cent had relapsed at 2½ years. The figure was higher for "open positives." And in "open negatives" *not* resected the relapse rate at 3½ years was 50 per cent—and almost 10 per cent were dead. With "closed negative" cases the figures were better: Eighty-eight of these, resected, showed a relapse rate of 12 per cent—4 years later. One hundred thirty-nine "closed negatives" *not* resected had a relapse rate of 19 per cent—3½ years later.

It is now four years since Hite and I[5] submitted a preliminary report on so-called "indefinitely prolonged chemotherapy"—with or without resection, depending on indications—and it is two years since our report[6]

*Remarks made in Round Table Luncheon discussion on this topic at the Interim Session, American College of Chest Physicians, Philadelphia, Pennsylvania, December 2, 1957.

of follow-up on 172 patients so-treated. At that time our relapses over a one to four year follow-up period came to 1.7 per cent. I cannot give you an up-to-the-minute report on these cases. Follow-up is being obtained, and we shall publish the figures as soon as we have them. Meanwhile, however, we have continued to treat patients, (now several hundred) indefinitely—whether resection has been done or not—because we have not yet found a reason to stop.

We know that residual lungs, after resection, contain viable tubercle bacilli. We know that unresected fibrocaseous lesions—"closed negatives" —as well as unresected cavities with negative sputum—so-called "open negatives"—contain living organisms. If these bacilli are in a resting state —not actively multiplying—we believe they are *at that moment* not susceptible to any known drug. Sterilization of the human lung by chemotherapy—of whatever duration—has not been demonstrated. But if, at the moment the bacilli re-awaken and begin again to multiply—(whether this occurs because of liquefaction or whether it itself causes liquefaction)—if at that time the tissues contain effective amounts of anti-bacterial drugs, further multiplication and liquefaction and bronchogenic spread are inhibited. Or so it appears.

The situation at this time seems comparable to the question of prophylaxis of rheumatic fever recurrences with penicillin. And like the American Heart Association *there*[7] we feel that *this* program should be continued until new knowledge (or drugs) makes it unnecessary. We do not have such knowledge as yet. We still see patients who have relapsed after chemotherapy was stopped—nor does the negativity of the sputum, the absence of cavity on tomography, or the small size of the original lesion seem to prevent. Nor are we seeing toxicity from drugs in any way comparable in importance to the risks of relapse.

I would say, then, that our present attitude, based on these considerations, is about this: Long-term results will apparently be best if chemotherapy is given uninterruptedly, if residual cavities after chemotherapy are excised (whether cultures are positive or negative) and if drug treatment is continued indefinitely.

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5 Dooneief, A. S. and Hite, K. E.: "Indefinitely Prolonged Chemotherapy for Tuberculosis," *Am. Rev. Tubere.*, 70:219, 1954.

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7 Statement by the Committee on Prevention of Rheumatic Fever and Bacterial Endocarditis, *Circulation*, 11:318, 1955.

ALFRED S. DOONEIEF, M.D., F.C.C.P.
Mt. Kisco, New York

Seymour M. Farber, M.D.
President
1959-1960

DR. SEYMOUR M. FARBER

Takes Office as College President

Seymour M. Farber was born on June 3, 1912 in Buffalo, New York, into a distinguished medical family. His undergraduate training was at the University of Buffalo where he received his B.A. degree in 1931. This was followed by graduate work in parasitology and medical studies at Harvard Medical School where he received his medical degree in 1939.

Dr. Farber joined the University of California Medical School faculty in 1942 as an Instructor in the Department of Medicine and has taught at that institution since then. At the present time, he is Chief of the University of California Tuberculosis and Chest Service at the San Francisco General Hospital and is Assistant Dean—In Charge of Continuing Education in Medicine and the Health Sciences at the University of California School of Medicine.

The research activities of Dr. Farber have been directed toward lung cancer, non-tuberculous chest diseases and clinical pulmonary physiology. He was one of the pioneers in the broad application of cytology to the diagnosis of chest diseases.

Dr. Farber's lectures have taken him to most parts of this country and to many countries in the world. His membership and appointments in medical societies reflect his broad interests and include being special consultant to the National Institutes of Health, Bethesda, Maryland, American Federation of Clinical Research, New York Academy of Sciences, Medical Advisory Cytology Committee, to name a few.

In rising to the Presidency of the American College of Chest Physicians and Chairman of the Section on Diseases of the Chest of the American Medical Association, Dr. Farber has devotedly served on numerous committees, councils and as an Associate Editor of *Diseases of the Chest*.

Dr. Farber is a member of many medical societies, including the San Francisco County Medical Society, California Medical Association, American Medical Association, California Society of Internal Medicine, New York Academy of Sciences, American Federation of Clinical Research, American Trudeau Society and the International Association of Medical Museums. He is a member of the Editorial Advisory Board for *GP*, the official journal of the American Academy of General Practice, has published over fifty articles in various medical journals and has written or contributed chapters to four books. A second edition of the book "Cytologic Diagnosis of Lung Cancer" is now in preparation.

Dr. Farber, his wife, the former Lynette True, and their three children, Burt, Margaret and Roy, live in San Francisco but spend a geat deal of time at their ranch outside of the city.

SILVER ANNIVERSARY MEETING

More than 1800 members and guests attended the 25th Annual Meeting of the American College of Chest Physicians held at the Ambassador Hotel, Atlantic City, New Jersey, June 3-7. This excellent registration represented almost every State in the Union and more than a dozen other countries. The quality of the scientific program was outstanding and the forty-one technical exhibits on display throughout the meeting attracted great interest.

The annual Convocation was held on Thursday evening, June 4th, when Fellowship Certificates were awarded to 215 physicians. Honorary Fellowship was conferred upon Dr. Harold S. Diehl, New York City, and upon Mr. Murray Kornfeld, Chicago, the Founder and Director of the American College of Chest Physicians. The degree of Master was conferred upon eleven Past-Presidents of the College. Distinguished guests present at the Convocation included Dr. Dwight L. Wilbur, San Francisco, Immediate Past-President of the American College of Physicians, Dr. Newell W. Philpott, Montreal, President of the American College of Surgeons, and Dr. Donald R. Wilson, Edmonton, representing the President of the Royal College of Physicians and Surgeons of Canada. Presiding officers were Dr. Donald R. McKay, Buffalo, President of the College, and Dr. John F. Briggs, St. Paul, Chairman of the Board of Regents. The Fourth Annual Louis Mark Lecture was presented at the Convocation by Dr. Briggs, and an address was given by the incoming President of the College, Dr. Seymour M. Farber, San Francisco. In a special ceremony during the Convocation, Dr. Mauricio Teichholz, Governor of the College for Rio de Janeiro, presented the Brazilian flag to the College for permanent display in the Executive Offices in Chicago, where flags of many nations represent College chapters throughout the world. This was the first College Convocation at which academic caps and gowns were worn, planned especially for the Silver Anniversary Meeting.

On Saturday evening, June 6th, the Annual Presidents' Banquet was held, preceded by a cocktail party honoring the Fathers and Sons in the College.

Dr. Donald R. McKay, President of the College, presided at the banquet and introduced the officials and special guests, as well as the Fathers and Sons and Charter Members of the College present. The banquet was attended by 590 physicians and members of their families.

The following congratulatory message was received from President Eisenhower and read by Dr. McKay:

Dr. Donald R. McKay, President
American College of Chest Physicians
Ambassador Hotel
Atlantic City, New Jersey

It is a pleasure to send greetings to those attending the Silver Anniversary Meeting of the American College of Chest Physicians.

The members of this organization have made important contributions to the diagnosis and treatment of chest diseases, both in our own country and throughout the world. In this tradition, I am sure they will continue to advance the health and welfare of mankind.

I am delighted to add my best wishes for a fine meeting.

Dwight D. Eisenhower

Congratulatory messages were also received from Governor Meyner of New Jersey, Governor Stratton of Illinois, and Mayor Daley of Chicago. The following was quoted by Dr. McKay from a letter received from Dr. Gunnar Gunderson, President of the American Medical Association:

> "The American College of Chest Physicians should take great pride in its accomplishments on the occasion of its Silver Anniversary. I can think of no field of medicine where such dramatic progress has been made as has been the accomplishment in conquering many of the conditions which existed in the thoracic cage prior to 25 years ago and were at that time untouchable or unremedial by either medicine or surgery. I hope that the next 25 years will be equally rich in accomplishments."

Dr. H. Allan Novack, Boston, chairman of the Committee on Prize Essay Awards, announced the winners of the 1959 College Essay Contest. The first prize winner, Michael A. Salmon, a student at Middlesex Hospital Medical School, University of London, could not be present. However, Mr. G. W. Aldington, C.M.G., Her Majesty's Consul General in Philadelphia, attended the banquet as a guest of the College and received for Mr. Salmon his certificate and cash award in the amount of $500.00 The title of the prize-winning essay was "Pulmonary Hydatidosis, a Review." Second prize was awarded to L. O. Baum, J. A. Murray and N. H. Oldham, of the Baylor University College of Medicine, who co-authored the essay entitled "Evaluation of Lung Volumes and Intrapulmonary Gas Mixing in Diseased and Normal Children." Both Mr. Murray and Mr. Oldham were present at the banquet and received from Dr. Novack their certificates of award and a check in the amount of $300.00. There was a tie for third place, the winners being Rose K. L. Wong of the University of Oregon Medical School, Portland, for her essay on "Postoperative Pulmonary Atelectasis" and Jack W. Hall of the Medical College of Virginia, Richmond, whose essay was entitled "Pulmonary Function Tests: Applications, Observations, Interpretations." Mrs. Wong and Mr. Hall, who were not able to be present at the banquet, will receive certificates of award and checks in the amount of $100.00 each, at appropriate ceremonies arranged by officials of the College in their home cities.

The 1959 College Medal was presented to Mr. Murray Kornfeld, Executive Director of the College, for having founded and developed the American College of Chest Physicians and the official journal, *Diseases of the Chest*, and for devoting 32 years of his life to the advancement of the specialty of diseases of the chest. Dr. Donald R. McKay, President, made the presentation.

The First Annual College Film Awards were presented by Dr. McKay, in the absence of Dr. Paul H. Holinger, Chicago, chairman of the Committee on Motion Pictures. The First Prize Certificate was presented to Dr. JD Mortensen, Latter-Day Saints Hospital, Salt Lake City, for his film "Surgical Repair of Atrial Septal Defect Utilizing the Atrial Well Technique." A Certificate of Merit was awarded to Dr. Arthur Vineberg, Montreal, Canada, for his film on "The Treatment of Coronary Arterial Heart Disease by Internal Mammary Artery Implantation." Other films selected by the judging committee to receive Certificates of Merit were: "Bronchocinematography" by Dr. Shogo Awataguchi, Research Institute for Tuberculosis and Leprosy, Tohoku University, Sendai, Japan; "Ventricular Aneurysm Following Myocardial Infarction: Surgical Excision Using Cardiopulmonary Bypass" by Dr. Denton A. Cooley, Baylor University College of Medicine, Houston; and "Resectional Procedures in Pulmonary Tuberculosis" by Dr. Ralph B. Lynn, University of Saskatchewan and Anti-Tuberculosis League of Saskatchewan, Saskatoon, Canada (presently at Queen's University, Kingston, Ontario.)

Dr. Burgess L. Gordon, Albuquerque, New Mexico, Immediate Past-President of the College, presented the Presidential Scroll to Dr. McKay and the College Past-President's Pin to Mrs. McKay.

Honored guests at the banquet were Dr. Harold S. Diehl, Senior Vice President for Research and Medical Affairs and Deputy Executive Vice President of the American Cancer Society; Dr. E. H. Christopherson, Executive Secretary of the American Academy of Pediatrics; Mr. E. R. Loveland, Executive Secretary of the American College of Physicians; Mr. William Stronach, Executive Director of the American College of Radiology; and Mr. Theodore Wiprud, Executive Director of the District of Columbia Medical Society.

Dr. McKay expressed the appreciation of the officers and members of the College to Drs. Arthur M. Master and Coleman B. Rabin, New York City, co-chairmen of the Committee on Scientific Program, and the members of their committee, for the preparation of an outstanding program; to Dr. Paul H. Holinger, Chicago, and the members of his Committee on Motion Pictures for the excellent film program; to Drs. J. J. Kirshner and William Likoff, Philadelphia, for arrangement of the postgraduate seminars, which were so well received; and to Dr. Irving Willner and the members of the New Jersey Chapter of the College for their cooperation in making the Silver Anniversary Meeting so successful.

Announcements were made of the Silver Anniversary Homecoming Meeting to be held in Albuquerque, New Mexico, October 14-17, 1959, the Interim Session of the College to be held in Dallas, Texas, November 29-30, 1959, and the 26th Annual Meeting which will be held in Miami Beach, Florida, June 8-12, 1960. Dr. McKay extended an invitation to the members and guests of the College to attend the Sixth International Congress on Diseases of the Chest, sponsored by the Council on International Affairs of the College, which is to be held in Vienna, Austria, August 28 through September 1, 1960.

The Ambassador Hotel, which has served as headquarters for annual meetings of the College five times in the past twelve years, prepared a special Silver Anniversary banquet program. Through the courtesy of United Airlines, baby vanda orchids from Hawaii were presented to the ladies attending the banquet. A dance closed the evening's activities.

Ladies Activities

The Ladies Reception Committee, under the chairmanship of Mrs. Charles Hyman, Atlantic City, planned an attractive program of activities for the ladies attending the Silver Anniversary Meeting of the College. On Thursday, June 4th, a luncheon was held at the Ritz-Carlton Hotel at which time dramatic presentations from plays by Eugene O'Neill were given by Mrs. John E. Devine. On Thursday evening the ladies attended the College Convocation. A sightseeing tour of Atlantic City and nearby townships, with a stop at a champagne factory, was planned for Friday. Following the tour, a luncheon was given at the Linwood Country Club. During lunch, musical selections were presented by Mr. Pedro Albani, accordionist. The annual College cocktail party, Presidents' Banquet and dance were held on Saturday evening, June 6th, which were attended by the ladies of the College. Mrs. Donald R. McKay, Mrs. Murray Kornfeld and Mrs. Irving Willner served as Honorary Chairmen of the Ladies Reception Committee.

Administrative Meetings

The Executive Council, Board of Regents and Board of Governors held their annual meetings in Atlantic City and matters of policy, as well as reports of the College councils and committees were discussed. The proceedings of these meetings and reports of councils and committees will be published in subsequent issues of *Diseases of the Chest*. All of the councils and committees of the College held their annual meetings on Thursday, June 4.

Reports of the President, Treasurer, Historian, Executive Director and the chairman of the Committee on Nominations were presented at the Open Administrative Session on Thursday, June 4th. The following officers for the year 1959-1960 were elected:

OFFICERS

President:	Seymour M. Farber, San Francisco, California
President-Elect:	M. Jay Flipse, Miami, Florida
1st Vice-President:	Hollis E. Johnson, Nashville, Tennessee
2nd Vice-President:	John F. Briggs, St. Paul, Minnesota
Treasurer:	Charles K. Petter, Waukegan, Illinois
Assistant Treasurer:	Albert H. Andrews, Chicago, Illinois
Historian:	Carl C. Aven, Marietta, Georgia
*Chairman, Board of Regents:	Arthur M. Olsen, Rochester, Minnesota
*Vice-Chairman, Board of Regents:	Irving Willner, Newark, New Jersey

*Elected by Board of Regents

REGENTS

District No. 1:	Edward A. Greco, Portland, Maine
District No. 3:	Ross K. Childerhose, Harrisburg, Pennsylvania
District No. 5:	Arnold S. Anderson, St. Petersburg, Florida
District No. 8:	Alfred Goldman, St. Louis, Missouri
District No. 10:	Johann L. Ehrenhaft, Iowa City, Iowa
District No. 13:	Elmer C. Rigby, Los Angeles, California
District No. 17:	Samuel J. Forrest, Toronto, Canada

GOVERNORS

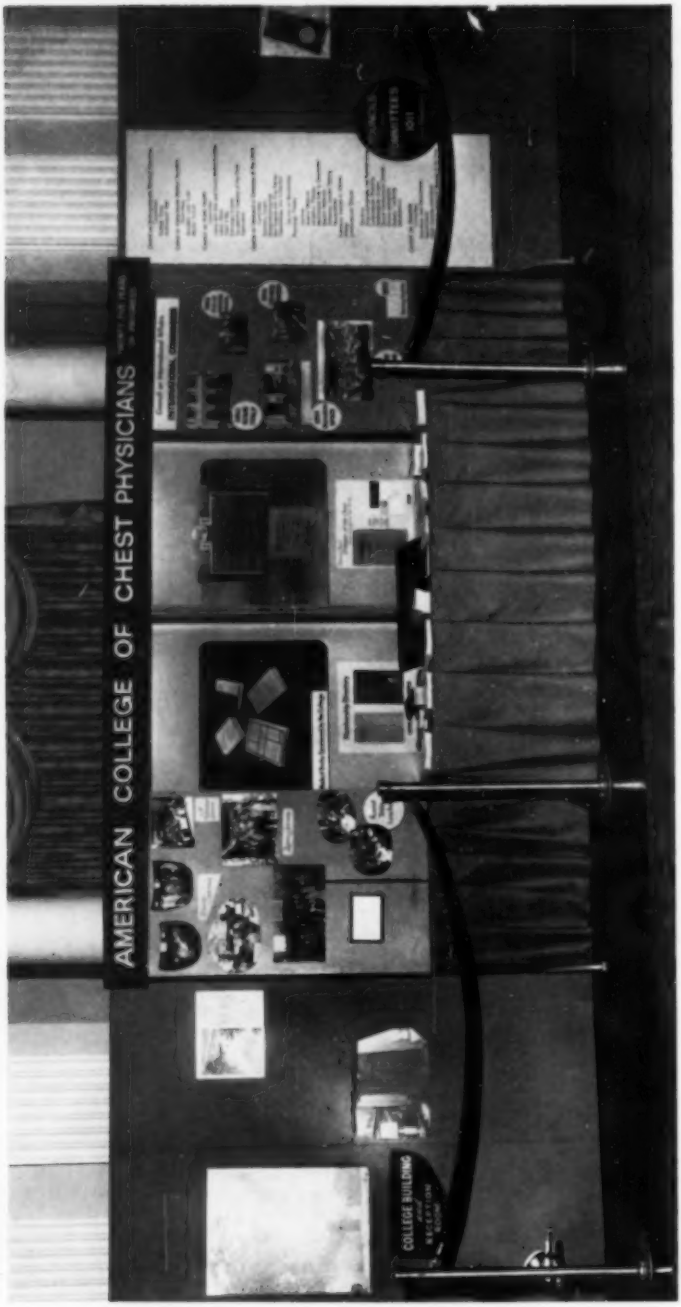
Arizona:	Howell S. Randolph, Phoenix
Arkansas:	William P. Gray, Batesville
Colorado:	W. Bernard Yegge, Denver
District of Columbia:	Edgar W. Davis, Washington
Florida:	Alexander Libow, Miami Beach
Hawaii:	William F. Leslie, Hilo
Idaho:	Kenneth A. Tyler, Gooding
Kansas:	Charles Pokorny, Halstead
Maine:	Albert Aranson, Portland
Maryland:	Otto C. Brantigan, Baltimore
New Jersey:	A. Albert Carabelli, Trenton
North Carolina:	Ralph E. Moyer, Oteen
North Dakota:	Paul J. Breslich, Minot
Pennsylvania:	Peter A. Theodos, Philadelphia
Texas:	Henry R. Hoskins, San Antonio
Virginia:	Everett C. Drash, Charlottesville
Washington:	Norman Arcese, Seattle
West Virginia:	George R. Maxwell, Morgantown

GOVERNMENT SERVICES

U. S. Army:	Brig. General Carl W. Tempel, Washington, D.C.
U. S. Navy:	Capt. Joseph M. Hanner, San Diego, California
U. S. Air Force:	Maj. Gen. Oliver K. Niess, Washington, D.C.
U. S. Veterans Administration:	Roy A. Wolford, Washington, D.C.
U. S. Public Health Service:	Robert J. Anderson, Atlanta, Georgia

CANADA

Maritime Provinces:	J. J. Quinlan, Kentville, Nova Scotia
Ontario:	John A. Lewis, London



The College Exhibit as displayed at the Silver Anniversary Meeting, Ambassador Hotel, Atlantic City, June 3-7, 1959.

Report of the Treasurer

STATEMENT OF INCOME AND EXPENSES FOR THE YEAR ENDED DECEMBER 31, 1958

INCOME:		
Annual Dues		$109,305.88
Fellowship Fees		23,012.50
Sales—		
Advertising	$44,843.81	
Subscriptions	33,229.26	
Exhibit Space	4,389.57	
College Services—Net	8,480.24	
	$90,942.88	
Less—Discount Allowed	10,354.39	80,588.49
Interest Received on U. S. Bonds		961.00
Interest on Investment and in Savings & Loan Associations		2,549.33
Contributions for College History		1,450.00
TOTAL INCOME		$217,867.20
EXPENSES:		
Salaries	$69,950.22	
Printing Journal	58,027.19	
Building Account	5,922.02	
Printing	6,081.21	
Handling and Posting Journal	6,138.06	
Postage and Shipping	3,895.40	
Translations	300.00	
Officers' and Committee Expense	3,478.55	
Telephone and Telegraph	3,184.51	
Office Expense	3,107.00	
Traveling—Executive Director	1,510.79	
Annual Meeting	10,406.46	
Interim Meeting—Board of Regents	2,104.74	
International Meeting	5,432.41	
Public Relations Expense	2,473.01	
Editorial Board	5,001.00	
Hospital Counselor	95.72	
College History	140.50	
Library Expense	311.90	
Membership Certificates	293.36	
Payroll Taxes	1,024.73	
Prize Essay Award	1,173.76	
Audit	400.00	
Contribution to World Medical Association	500.00	
College Medals	87.90	
Contribution to National Society for Medical Research	25.00	
Directory—Net	13,854.21	
Depreciation—Furniture and Fixtures	1,808.89	
Total Expenses		206,728.54
NET INCOME		$ 11,138.66

Ralph H. Marcus, Certified Public Accountant, Chicago, Illinois

Charles K. Petter, *Treasurer*

Committee on Nominations

The Committee on Nominations for the 1960 annual College elections is composed of Dr. Burgess L. Gordon, Albuquerque, New Mexico, Chairman, elected to the committee by the Board of Regents, Dr. George R. Maxwell, Morgantown, West Virginia, elected by the Board of Governors, and Dr. Jack Reiss, Coral Gables, Florida, appointed by the President.

Recommendations for elective offices may be addressed to Dr. Burgess L. Gordon, Chairman, 4902 Constitution Avenue, N. E., Albuquerque, New Mexico. The Committee on Nominations will meet in Dallas, Texas, on November 29, 1959, during the Interim Session of the College.

Committee on Scientific Program for 1960 Meeting Requests Abstracts of Papers

Miami Beach, Florida will be host to the 26th Annual Meeting of the College, June 8-12, 1960. Plans for the scientific program are now under way and physicians interested in presenting papers are invited to submit a 200-word abstract to the appropriate committee chairman for consideration. Abstracts may be forwarded directly to one of the following co-chairmen:

Major General Thomas W. Mattingly, Washington Hospital Center, Washington, D.C., Chairman, Section on Cardiovascular Diseases
Dr. R. Drew Miller, Mayo Clinic, Rochester, Minnesota, Chairman, Section on Pulmonary Diseases

Committee on Motion Pictures

The Committee on Motion Pictures of the College is interested in learning of new films on diseases of the chest (heart and lung) for possible presentation at the 26th Annual Meeting of the College in Miami Beach. All pertinent information concerning films may be forwarded to Dr. Paul H. Holinger, chairman of the committee, 112 East Chestnut Street, Chicago 11, Illinois. Those accepted for presentation in the annual motion picture program will be eligible for the 1960 Film Contest and will be referred to the judging committee for review. The Committee on Motion Pictures will also be pleased to review films for official approval and inclusion in the Approved Film List of the American College of Chest Physicians.

Chapter News

SOUTHERN CHAPTER OF SOUTH AFRICA

The 100th meeting of the Southern Chapter of South Africa was held in Cape Town on April 20. This chapter is one of the most active in the College and has been influential in developing medical activities in the Cape Town area. Dr. Silber, Lecturer at the University of Cape Town, presented a paper on "Benign Conditions of the Esophagus, with Remarks on Developmental Anatomy." The lecture was followed by a discussion.

The following chapter officers were re-elected:

President:	David P. Marais, Cape Town
Vice President:	Theodore Shrire, Cape Town
Secretary:	Hendrik Muller, Cape Town
Treasurer:	Michael J. Bailey, Cape Town

NEW CHAPTER OFFICERS

BAHIA CHAPTER OF BRAZIL

President:	Adelaido Ribeiro, Salvador
Secretary-Treasurer:	Itazil Benicio dos Santos, Salvador

ISRAELI CHAPTER

President:	Arthur Freund, Tivon
President-Elect:	Joseph Rakower, Jerusalem
Secretary-Treasurer:	Wilhelm J. Huppert, Kfar Saba

MICHIGAN CHAPTER

President	Nathan Levitt, Detroit
Vice-President:	James T. Cheng, Pontiac
Secretary-Treasurer:	Arthur J. Vorwald, Detroit

News Notes

Dr. Herman J. Moersch, Mayo Clinic, Rochester, Minnesota, past-president of the American College of Chest Physicians, received the Rudolph Schindler Award for outstanding achievement in the field of gastroscopy of the American Gastroscopic Society on June 7th. The award was presented by **Dr. Arthur M. Olsen,** also of the Mayo Clinic, at the annual meeting of the Society in Atlantic City.

Dr. David State, formerly of Los Angeles, has been named Professor and Chairman, Department of Surgery, Albert Einstein College of Medicine, New York City.

Dr. Benjamin M. Gasul, Chicago, recently spoke before the Puerto Rico Chapter of the College on "Recent Advances in the Diagnosis of Congenital Heart Disease." Dr. Gasul held clinics at the request of the chapter and the Puerto Rico Pediatric Society.

Dr. William Likoff, Philadelphia, Pennsylvania, has been appointed Director of the Cardiovascular Section, Hahnemann Medical College and Hospital.

Dr. Ihsan Rifat Sabar, Istanbul, Turkey, was recently promoted to the Chair of Professor of Phthisiology and Director, Phthisiological Clinical of the University of Istanbul.

Dr. John L. Keeley, Chicago, has been appointed Professor and Chairman of the Department of Surgery at the Stritch School of Medicine of Loyola University.

Drs. Richard H. Overholt, Boston, **Max S. Sadove,** Chicago, and **John Keshishian,** Washington, D. C. have volunteered their services to MEDICO to take part in an emergency mission to Viet Nam to clear up a backlog of pulmonary tuberculosis cases which threaten to overwhelm medical facilities there. Drs. Overholt and Sadove arrived in Saigon on April 1 for a two-month stay and Dr. Keshishian plans to be there from June 15-August 15.

Dr. Jose Ignacio Baldo, Caracas, Venezuela, Regent of the College for Venezuela, has been appointed Chief of the Department of Chronic Diseases at the Ministry of Public Health.

Dr. William B. Bean, Iowa City, Iowa, has been named a Regent to the National Library of Medicine by President Dwight D. Eisenhower. He will serve for a period of four years.

Dr. Charles A. Hufnagel, Washington, D. C. was selected by the Executive Board of the Medical Society of the District of Columbia to present the 1959 George M. Kober Lecture of Georgetown University School of Medicine. Dr. Hufnagel spoke on "The Basic Concepts of Cardiac and Vascular Reconstruction."

Dr. C. Walton Lillehei, Minneapolis, Minnesota, has been named an honorary member of the International Medical Club for his accomplishments in cardiovascular surgery. The announcement was made at the annual meeting of the American Association for the Advancement of Science in Washington, D.C.

ANNOUNCEMENT

The Israel Association of Chest Physicians will hold a meeting in Jerusalem, Israel, September 22-23 and the subject "Epidemiological Problems of Tuberculosis" will be discussed. Organized tours of the Holy Land will be included in the program. Applications for registration may be sent to: Israel Association of Chest Physicians, P.O. Box 8123, Jaffo, Tel Aviv, Israel.

Book Review

Weiller, Pierre, AVIATION ET TUBERCULOSE PULMONAIRE, with preface by Prof. Robert Monod, Vigot Frères, Éditeurs, Paris, 1958. 232 Pages, 22 Figures.

Dr. Weiller discusses the problems of air travel in patients with suspected or unsuspected pulmonary tuberculosis in considerable detail. His survey of the literature is excellent and he reports a large number of individual cases. As might be expected, he devotes a considerable part of his study to collapse therapy, particularly air replacement in type. Although little new is reported, the clinical approach to the problem may interest those concerned with it. So far as the effects of flying on lesions is concerned, the occurrence of unfavorable responses is not so large as to cause concern. His eventual conclusion is the same as MacFarland's:—"If you can walk you may fly," although certain reservations must be made.

Roger H. L. Wilson, M.D.

CALENDAR OF EVENTS

National Meetings

Homecoming Meeting

Silver Anniversary, American College of Chest Physicians
Albuquerque, New Mexico, October 14-17, 1959

Interim Session

American College of Chest Physicians
Dallas, Texas, November 29-30, 1959

Postgraduate Courses

14th Annual Course, "Clinical Cardiopulmonary Physiology"
Chicago, Illinois, October 5-9, 1959

12th Annual Course on Diseases of the Chest
New York City, November 9-13, 1959

5th Annual Course on Diseases of the Chest
Los Angeles, California, December 7-11, 1959

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